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American Heart Journal

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Original Communications

LEFT ATRIAL AND PULMONARY "CAPILLARY" PRESSURE CURVES DURING VALSALVA'S EXPERIMENT

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SIMULTANEOUS recordings of the left atrial and pulmonary "capillary" pressures in man, with the chest wall intact,[1] have demonstrated that in most subjects the pressure curves from the pulmonary "capillaries" closely resemble those from the left atrium. We are unable, therefore, to accept Burton's[3] suggestion that the term "capillary pressure" be abandoned and this pressure be called the "impacted small artery pressure." A more logical designation might be the "reflected left atrial pressure." However, for the present there would seem to be no reason for abandoning the term "pulmonary capillary pressure" introduced by Dexter and associates.[5]

This communication is concerned with simultaneous measurements of the left atrial and pulmonary "capillary" pressures during brief periods of raised intrathoracic pressure produced by the Valsalva maneuver in nine patients with mitral valve disease.

METHODS

The pulmonary "capillary" pressure (PC) was recorded by the method of Dexter and his co-workers,[5] and the left atrial pressure (LA) by Björk's technique of direct right paravertebral puncture of the left atrium.

The patient was instructed to inspire deeply and then expire forcibly against the closed glottis or through a bottle containing mercury.

The pressures were recorded with a Hansen-Warburg capacitance manometer. The mean pressures were determined by planimetric integration of the area between the pressure curve and the base line.

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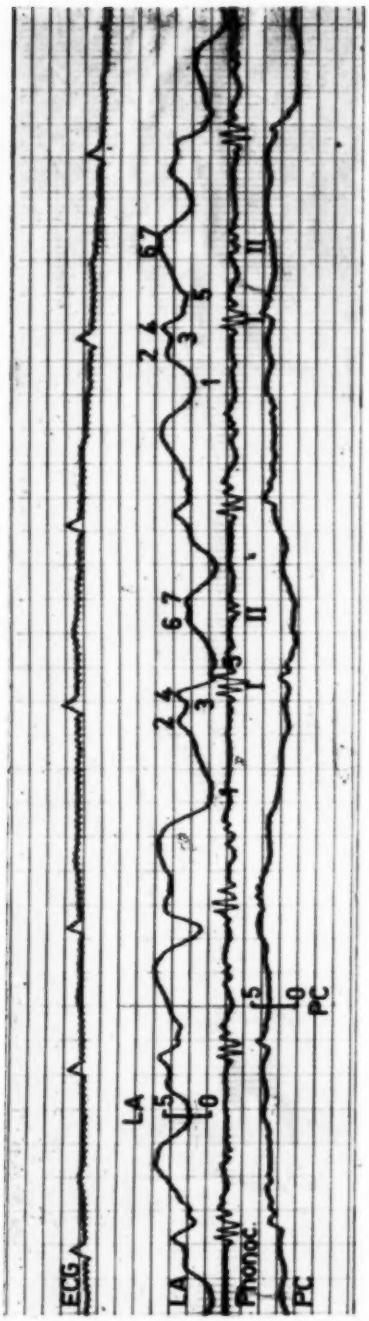


Fig. 1.—Pressure curves from a case with normal mitral valves. In this and subsequent figures the following abbreviations are used: *LA* = left atrium; *PC* = pulmonary "capillaries"; *ECG* = electrocardiogram; *PCG* = phonocardiogram; *I* = first heart sound; *II* = second heart sound. The phases of the cardiac cycle are indicated by number 1 through 7: *1-2-3* = contraction of the atrium; *3-4* = closure of the mitral valve; *4-5* = downward movement of the base of the left ventricle; *6* = closure of the aortic valve; *7* = opening of the mitral valve.

RESULTS

1. The left atrial and pulmonary "capillary" pressure curves in a case with normal mitral valves are illustrated in Fig. 1.

2. In patients with mitral stenosis the Valsalva maneuver led to increased intrathoracic pressure which immediately caused a simultaneous elevation of the left atrial and pulmonary "capillary" pressures (Fig. 2, A and B).

3. The increase in pressure, i.e., the difference between the mean pressure before and that during forced expiration, was of the same order in both the pulmonary "capillary" and the left atrial curves (see Table I).

TABLE I. SIMULTANEOUS LEFT ATRIAL (LA) AND PULMONARY "CAPILLARY" (PC) MEAN PRESSURES IN MILLIMETERS OF MERCURY BEFORE AND DURING THE VALSALVA MANEUVER AS WELL AS THE PULMONARY ARTERY (PA) PRESSURE AT REST

CASE NO.	LA PRESSURE			PC PRESSURE			PA PRESSURE		
	BEFORE	DURING	DIFF.	BEFORE	DURING	DIFF.	S	D	M
1.	23.5	45.5	22	19	47	28	86	59	70
2.	11	48	37	11.5	49.5	38	29	17	22.5
3.	14.5	38.5	24	15.5	40	24.5	37	21	27
4.	14	33	19	24	51	27	114	57	78
5.	24	47	23	26	52	26	74	28	47.5
6.	19	58.5	39.5	21	56	35	55	26	38
7.	11	33.5	22.5	11	29	18	31	15	22
8.	19.5	43.5	24	14.5	46	31.5	42	18	27
9.	21	59	38	23.5	62	38.5	29	18	23.5
		Mean	27.7		Mean	29.6			

S = systolic; D = diastolic; M = mean.

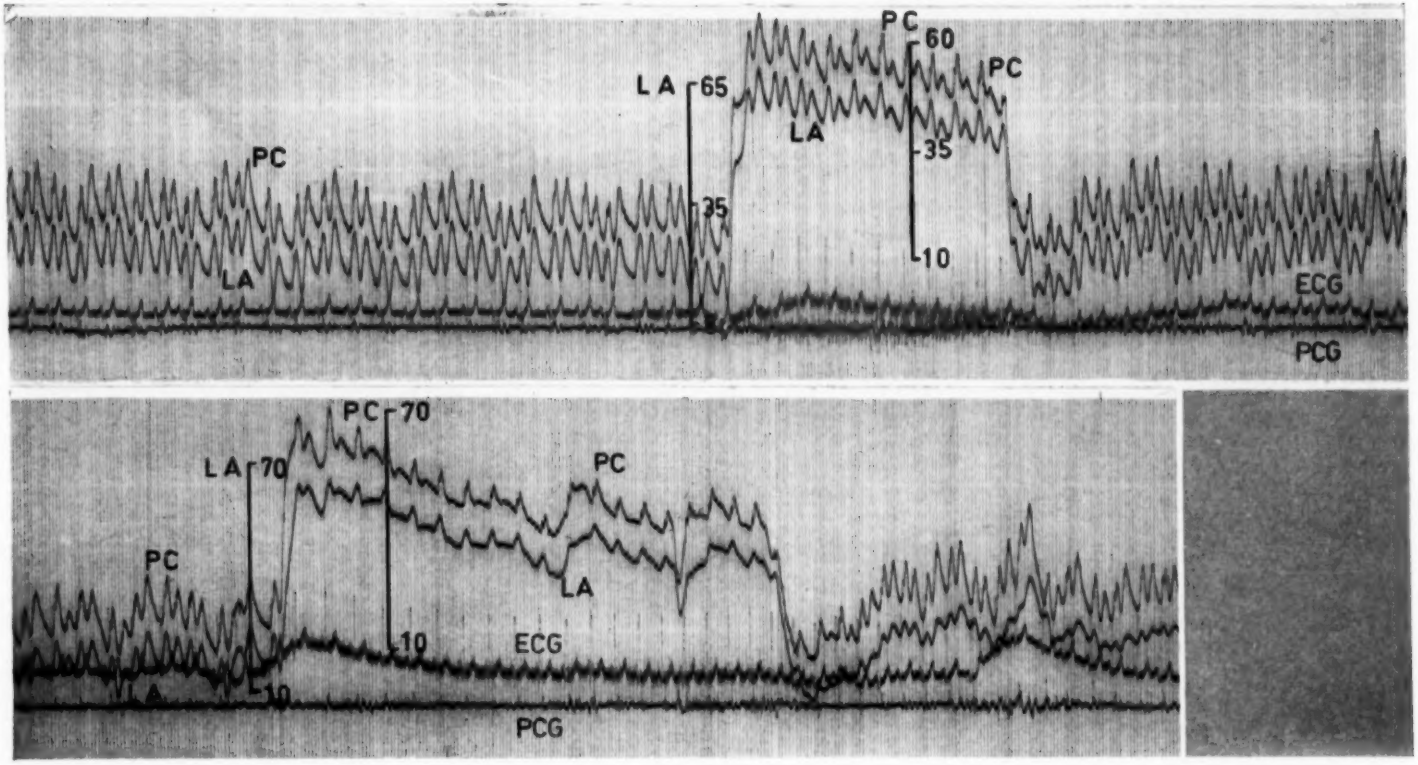
4. As forced expiration continued there was a decline in both the left atrial and the pulmonary "capillary" pressures (Figs. 2, 3, and 4). This was of the same magnitude in the two curves. The mean pressures at the beginning and toward the end of forced expiration in some of the experiments are shown in Table II.

TABLE II. SIMULTANEOUS LEFT ATRIAL AND PULMONARY "CAPILLARY" PRESSURES IN MILLIMETERS OF MERCURY AT THE BEGINNING AND TOWARD THE END OF THE VALSALVA MANEUVER

CASE NO.	LEFT ATRIAL PRESSURE			PULMONARY "CAPILLARY" PRESSURE		
	BEGINNING	TOWARD END	DIFF.	BEGINNING	TOWARD END	DIFF.
5 a.	62	36	26	67.5	39.5	28
b.	53.5	40	13.5	61	42.5	18.5
c.	72	56	16	71	53	18
6.	68	58.5	9.5	67.5	47	20.5

5. Throughout the maneuver the shape of the pulmonary "capillary" pressure curve paralleled that of the left atrial pressure curve.

A.



B.

Fig. 2.—*A* and *B*. Simultaneous left atrial (*LA*) and pulmonary "capillary" (*PC*) pressures before, during, and after two Valsalva maneuvers in a patient with mitral stenosis (Case 6). After the end of forced expiration there is an abrupt fall in pressures to below the normal values, followed by a gradual rise and overshoot. In record *B* the maneuver is of longer duration than in record *A*. This causes a more pronounced overshoot of the pressure in the postexpiration period.

6. In several subjects there was a gradual decrease in the pulmonary "capillary" pulse pressure contour during forced expiration, the amplitude in some instances falling almost to zero toward the end of the maneuver (Fig. 4).

7. In the left atrial pressure curve the amplitude of peak 2-4 remained practically the same throughout the maneuver. This amplitude represents the atrial systolic pressure, and in patients with sinus rhythm is the result of contraction of the atrium and closure of the mitral valve. The amplitude of peak 7, representing opening of the mitral valve, showed, on the other hand, a continuing decrease during the maneuver, and in many instances dropped almost to zero toward the end. During the third and fourth beats after forced expiration was ended, the peak regained its normal amplitude (Table III and Fig. 3, A and B).

TABLE III. CASE 6. SIMULTANEOUS LEFT ATRIAL (LA) AND PULMONARY "CAPILLARY" (PC) PRESSURES BEFORE, DURING, AND AFTER ONE VALSALVA MANEUVER

	PEAK 2-4		PEAK 7	
	LA	PC	LA	PC
Before the Valsalva maneuver	11.3	6.5	16	10
At the beginning of Valsalva maneuver	12.3	10.1	5.6	5.6
Toward the end of Valsalva maneuver	8.9	8.6	1.4	2.1
Immediately after Valsalva maneuver	10.7	8.0	5.4	2.4
3.2-5.8 seconds after maneuver	12.2	10.6	15.3	11.2
13.2-15.5 seconds after maneuver	12.1	11.5	14.9	11.0
Later	10.6	11.1	16.0	11.0

Peak 2-4 pressure denotes the difference between the pressures at point 1 (presystole) and point 2-4 (contraction of left atrium and closure of mitral valve). Peak 7 pressure denotes the difference between the pressures at point 5 and point 7 opening of the mitral valve. Values in millimeters of mercury.

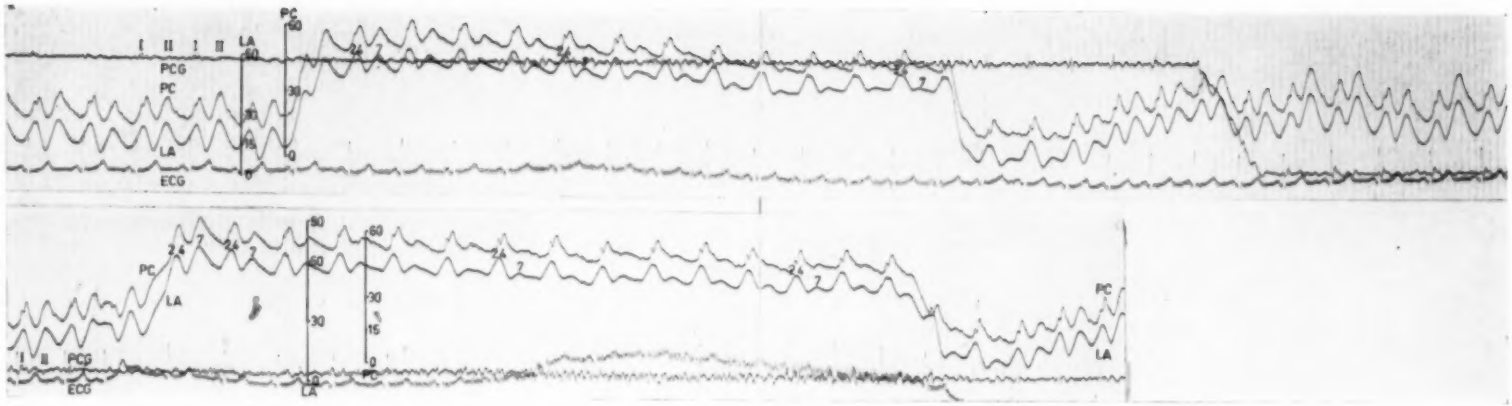
In Table III are shown the amplitudes of the peaks in millimeters of mercury immediately preceding, during and at various intervals after the maneuver in Case 6. It can be seen from the table that (a) the pressure changes in the pulmonary "capillary" curve paralleled those in the left atrial curve, (b) the fall in the amplitude of peak 7 greatly exceeded that in peak 2-4.

TABLE IV. CASE 6. SIMULTANEOUS LEFT ATRIAL (LA) AND PULMONARY "CAPILLARY" (PC) PRESSURES BEFORE, DURING, AND AFTER ONE VALSALVA MANEUVER

	POINT 1		POINT 2-4		POINT 5		POINT 7	
	LA	PC	LA	PC	LA	PC	LA	PC
Before Valsalva's maneuver	20.6	19.6	31.9	26.1	16.6	19.1	32.6	29.1
At the beginning of maneuver	64.5	53.6	76.8	63.7	65.2	54.8	70.8	60.4
Toward the end of maneuver	54.5	43.9	63.4	52.5	54.8	44.7	56.2	46.8
Immediately after maneuver	16.4	15.4	27.1	23.4	12.6	14.2	18.0	16.6
3.2-5.8 seconds after maneuver	33.0	28.6	45.2	39.2	35.2	30.5	50.5	41.7
13.2-15.5 seconds after maneuver	24.4	20.7	36.5	32.2	21.9	22.5	36.8	33.5
Later	21.2	17.5	31.8	28.6	16.9	18.4	32.9	29.4

Point 1 = presystole; Point 2-4 = summation of contraction of left atrium and closure of mitral valve; Point 4-5 = downward movement of base of ventricle; Point 7 = opening of mitral valve. Values in millimeters of mercury.

A.



B.

Fig. 3.—*A* and *B*. Simultaneous left atrial (*LA*) and pulmonary "capillary" (*PC*) pressures before, during, and after two Valsalva maneuvers in Case 6. In both the records *A* and *B*, peak *2-4* maintains practically the same amplitude throughout the maneuver while peak *7* gradually declines. After forced expiration is ended there is an abrupt fall in the pressures to below the normal values, followed by a gradual rise and pressure overshoot.

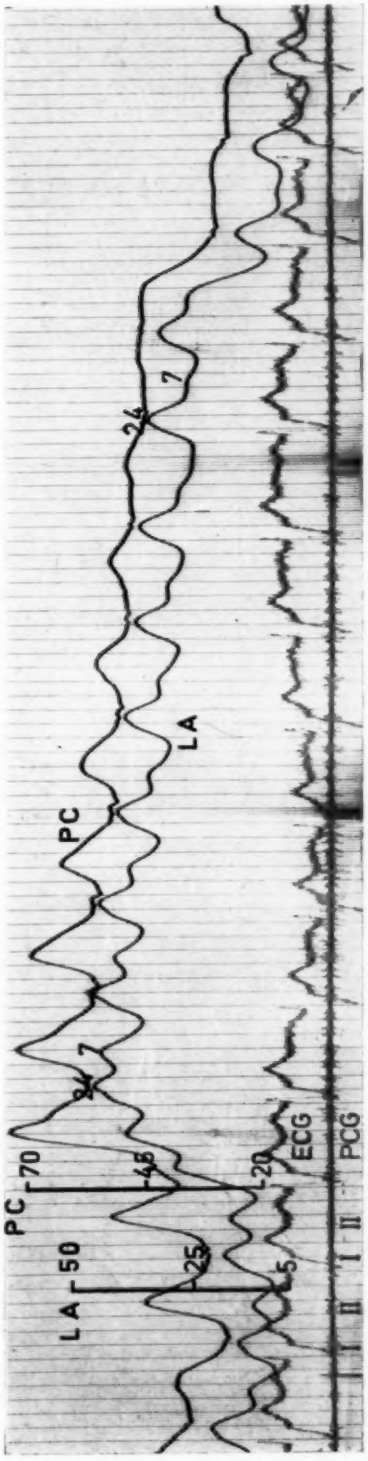


Fig. 4.—Simultaneous left atrial (*LA*) and pulmonary "capillary" (*PC*) pressures during the Valsalva maneuver in a patient with pure mitral stenosis (Case 4). Note that the amplitude of the pulmonary "capillary" pressure gradually declines and toward the end of the maneuver falls to almost zero. In the left atrial curve, peak 2-4 maintains practically the same amplitude throughout the maneuver, while the amplitude of peak 7 gradually declines.

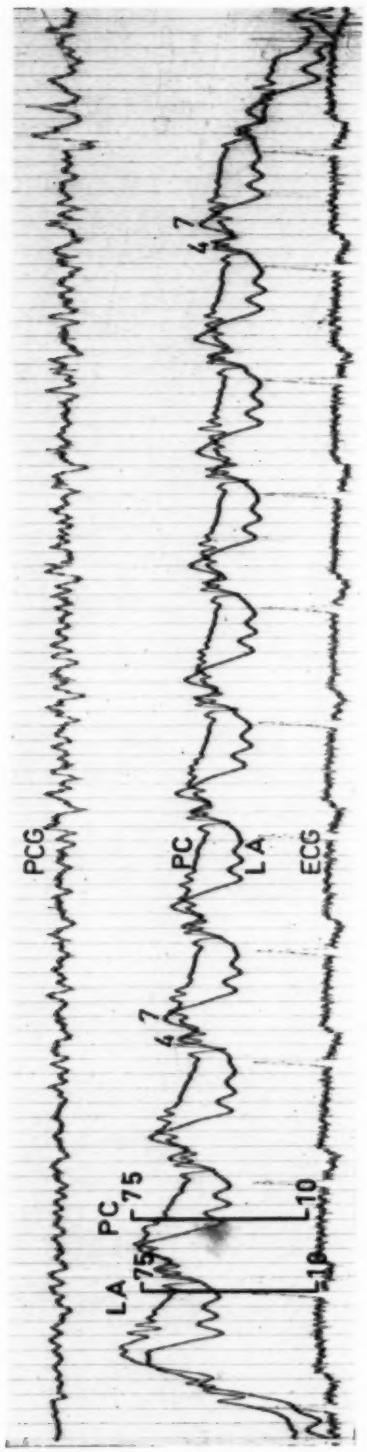


Fig. 5.—Simultaneous left atrial (*LA*) and pulmonary "capillary" (*PC*) pressures during the Valsalva maneuver in a patient with mitral stenosis combined with clinically significant regurgitation (Case 5). Note that peak 7 maintains practically the same amplitude throughout the maneuver.

8. After forced expiration was ended the intrathoracic pressure fell abruptly. This was accompanied by a simultaneous fall in the pulmonary "capillary" and left atrial pressures to below the resting values. This was followed by a rapid rise until during the third and fourth beats the systolic pressure rose above the resting value and there was an overshoot (Fig. 2, A and B).

In Table IV are shown the pulmonary "capillary" and left atrial pressures prior to, during, and after one Valsalva maneuver in Case 6. The mean left atrial pressure at rest was 26 mm. Hg and after the maneuver 18.5 mm. Hg. This fall in pressure was followed by a rapid rise and overshoot to 42 mm. Hg and, finally, a gradual return to normal.

In only one patient was there a time lag of approximately 0.1 sec. between the fall in the left atrial pressure and that in the pulmonary "capillary" pressure (Fig. 4).

DISCUSSION

Simultaneous measurements of the left atrial and pulmonary "capillary" pressures during the Valsalva maneuver have been done in patients with mitral valve disease.

In every instance the shape of the pulmonary "capillary" curve paralleled that of the left atrial pressure curve both during and after forced expiration.

In both curves the level of the pressure plateau was somewhat lower at the end of the maneuver than at the beginning. This fall in atrial pressure is presumably due to the arrest of blood in the venous system and a consequent reduction in blood flow through the lungs. The fall in the left atrial pressure was paralleled in the pulmonary "capillary" pressure.

The pulse pressure contour is considerably diminished during the Valsalva maneuver. In the left atrial pressure curve the amplitude of peak 2-4, representing contraction of the atrium and closing of the mitral valve, is slightly diminished during forced expiration while that of peak 7, representing opening of the mitral valve, is generally considerably diminished. In mitral stenosis without significant regurgitation, peak 7 is the result of pulmonary venous return to the atrium, accompanied possibly by upward movement of the base of the ventricle. During forced expiration there is a reduction in venous return to the left atrium and a consequent reduction in ventricular filling. This causes a corresponding fall in the amplitude of peak 7, in some instances almost to zero.

In patients showing a left atrial pressure pattern characteristic of mitral stenosis combined with marked regurgitation, causing a highly elevated peak 7, there is a slight fall in the peak amplitude during forced expiration, but never to the same degree as in cases without regurgitation (Fig. 5).

Therefore, in patients without mitral regurgitation, the reduction in the amplitude of peak 7 is presumably due partly to a reduction in venous return to the left atrium and partly to a decrease in the amount of regurgitated blood, the result of diminished stroke volume. In patients with a marked degree of mitral regurgitation peak 7 will probably maintain its high amplitude throughout the maneuver.

The amplitude of the pulmonary "capillary" pulse pressure contour is considerably reduced toward the end of forced expiration. In a few cases in this series the waves that remained were very small, especially in patients with a relatively low pulse pressure. It is obvious that increased intrathoracic pressure will primarily affect the pulmonary "capillary" pressure and produce a damped curve as compared with the left atrial pressure curve.

Following the cessation of forced expiration, there is an abrupt fall in the pressure to below the resting value. The release of the blood arrested in the venous system causes a sudden increase in the pulmonary flow and a consequent increase in the left atrial pressure that is maintained for a prolonged period. In one patient this overshoot lasted for more than 16 seconds. All the changes in the left atrial pressure curve enumerated here were paralleled in the concomitant pulmonary "capillary" pressure curve.

None of the patients showed a bradycardia during the period of forced expiration. A slight increase in the mean left atrial pressure was observed in similar experiments of one to two hours duration, even when the Valsalva maneuver was not applied.

SUMMARY

Simultaneous measurements of the left atrial and pulmonary "capillary" pressures were made during the Valsalva maneuver in nine patients with mitral valve disease.

1. The pulmonary "capillary" pressure curve paralleled the left atrial pressure curve both during and after the period of forced expiration.
2. There was a decline in the pressure during the Valsalva maneuver.
3. A pronounced decrease in the amplitude of peak 7 (representing opening of the mitral valve) during forced expiration was observed in all but one of the patients. In this patient mitral regurgitation was suspected and here the decrease in amplitude was less pronounced.
4. After forced expiration was ended the pressures fell abruptly to below the resting values. This was followed by a rapid rise and overshoot above the normal levels. This overshoot phenomenon is attributed to the sudden increase in the pulmonary flow that follows release of the blood arrested in the venous system during the Valsalva maneuver.

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THE CLINICOPATHOLOGIC CORRELATION OF LUNG BIOPSIES IN MITRAL STENOSIS

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THERE are two pathologic sources of obstruction to blood flow in mitral stenosis. The primary obstruction results from narrowing of the mitral valve and the pathologic changes are well known. Secondary obstruction occurs in the pulmonary vessels. The histologic changes in the lungs were first described by Parker and Weiss[1] and recently emphasized by Larrabee and associates[2] and by Henry.[3]

Lewis and associates[4] have correlated the clinical and cardiac catheterization findings with the degree of anatomic stenosis of the mitral valve. The present report will deal with the correlation of clinical and cardiac catheterization findings with the pathologic findings in the lungs obtained by biopsy at the time of mitral valvulotomy.

Recent operative procedures upon the diseased valve have attempted to restore valvular action and have effectively relieved that source of obstruction. Larrabee and associates[2] have pointed out that the structural changes in the lungs would have to be considered in order to determine whether such an operation would benefit the patient in the event that organic pulmonary changes had already developed. If there is a zone of high resistance to pulmonary flow at the level of the intrapulmonary arteries and arterioles, it is logical to assume that this resistance would place a continued strain on the right ventricle and ultimately lead to failure of that organ even if the obstruction at the mitral valve had been relieved. They have postulated that once intimal fibrosis of the smaller pulmonary arteries and arterioles has developed the resultant luminal narrowing might well be permanent, and that were such changes widespread, increased resistance to pulmonary blood flow would continue even though the stenotic lesion of the mitral valve had been corrected. They also pointed out that little benefit would be expected in cases in which the thickened media was scarred, since scarred arteries and arterioles probably would be incapable of dilating. They further postulated that a vessel wherein the only change was hypertrophy of the media might be capable of considerable dilatation after the stenotic condition

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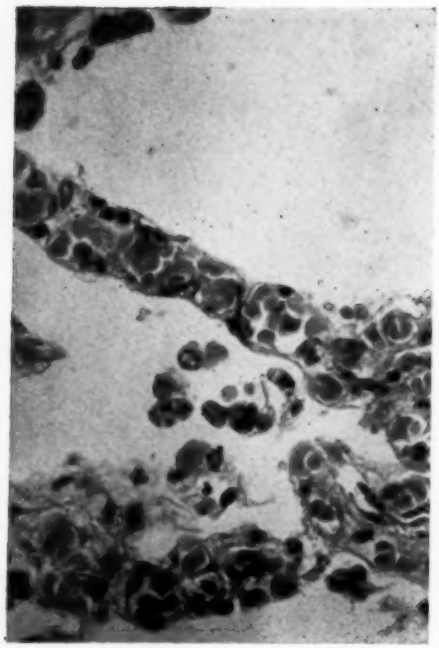

Fig. 1

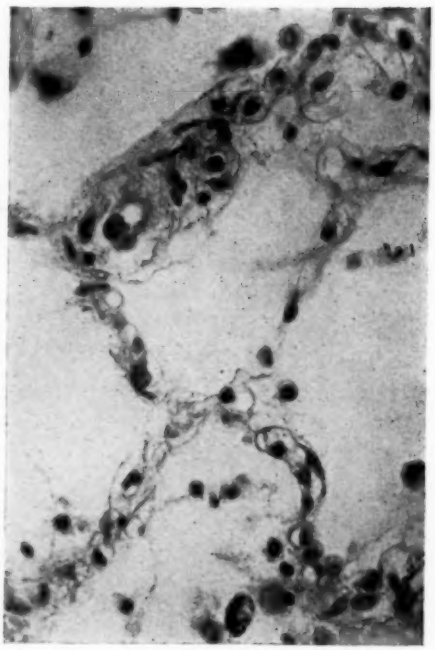

Fig. 2

Fig. 1.—Marked dilatation and congestion of alveolar capillaries. Hematoxylin and eosin stain. (×800; reduced ⅓.)

Fig. 2.—Pericapillary edema. Masson's trichrome stain. (×800; reduced ⅓.)

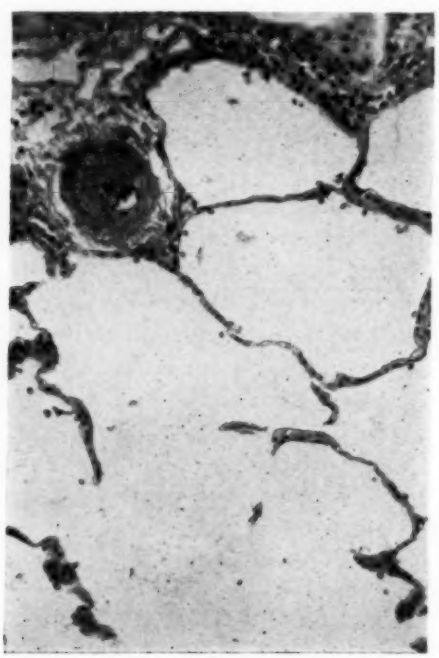

Fig. 3.—Emphysema with patchy fibrosis of alveolar wall and arteriole with markedly thickened wall. Hematoxylin and eosin stain. (×300; reduced ⅓.)

in the mitral valve had been overcome. They also thought that medial hypertrophy was probably one of the earliest organic changes and that intimal fibrosis and medial scarring probably develop later. Because previous studies were all based on autopsy material from cases who died of mitral stenosis it seemed pertinent to us to study the pulmonary changes in biopsy material removed from the lung at the time of mitral valvulotomy in patients in various stages of their disease. In an attempt to select the patients who might have far advanced pulmonary changes, we have attempted to correlate the pathologic findings in the biopsy specimen with the clinical findings obtained by history, physical examination, electrocardiogram, chest roentgenogram, and cardiac catheterization.

MATERIAL AND METHODS

A wedge of pulmonary tissue from the lingula was resected at the time of mitral valvulotomy and examined in each of fifteen consecutive patients with mitral stenosis as the only significant valve lesion. Sections of the lung tissue were stained with hematoxylin and eosin, with Masson's trichrome, and with Verhoeff's stain for elastic tissue, counter-stained with van Gieson's stain for connective tissue. Qualitative histologic study was made of both the alveolar and vascular tissues. For control purposes random autopsy material from ten patients without cardiac or pulmonary disease was selected.

Clinical factors evaluated were age, duration of disease or symptoms, the clinical status of the patient according to the classification of Harken and associates,[5] the appearance of the lung fields on a 2-meter chest roentgenogram, the electrocardiographic evidence of right ventricular hypertrophy according to the criteria of Myers and associates,[6] the resting pulmonary artery and "capillary" pressures, and the total pulmonary and pulmonary arteriolar resistances using the formulas of Dexter and associates.[7]

RESULTS

The alveolar changes consisted of dilatation and congestion of the capillaries, pericapillary edema, thickening of the capillary basement membrane, increase in the interstitial connective tissue, and the presence of pigmented macrophages in the alveolar spaces. Emphysema was found in scattered areas and in some areas the alveolar epithelium had assumed a cuboidal form. The alveolar walls were narrowed but contained a definite increase of the interstitial connective tissue and where this was marked many of the capillaries were obliterated. The alveolar changes were arbitrarily graded from zero to four-plus, zero being within normal limits and four-plus showing marked changes. These changes are shown in Figs. 1 to 3.

The changes in the pulmonary arterioles consisted of fibrous and intimal thickening and medial muscular hypertrophy with definite narrowing of the lumen. The large and medium-sized arteries showed intimal fibrosis, and splitting of the internal elastic lamina was also observed. There appeared to be no significant changes in the veins except for thickening and fibrosis of the perivascular collagen. In none of our patients was there any evidence of arteritis

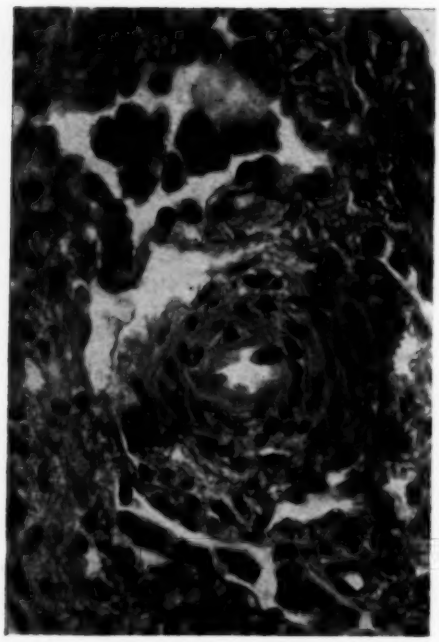

Fig. 4

Fig. 5

Fig. 4.—Marked medial muscular hypertrophy of arteriole; cuboidal epithelial lining of alveoli and pigment macrophages in alveolar space. Hematoxylin and eosin stain. (×800; reduced ½.)

Fig. 5.—Medial muscular hypertrophy of arteriole. Hematoxylin and eosin stain. (×800; reduced ½.)

Fig. 6

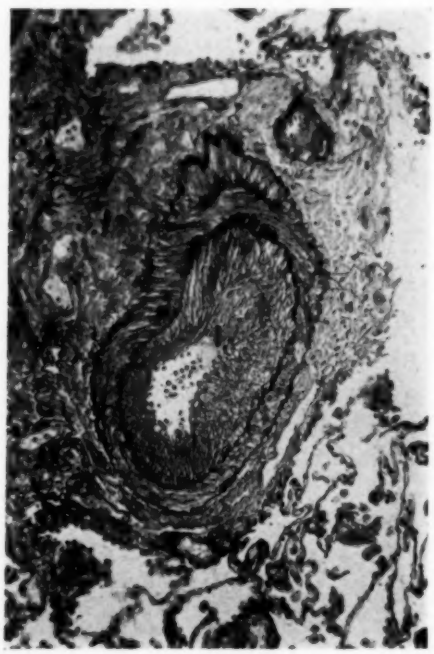

Fig. 7

Fig. 6.—Muscular hypertrophy of arteriole and marked interstitial fibrosis. Verhoeff stain. (×800; reduced ½.)

Fig. 7.—Medium-sized artery with marked intimal fibrosis. Verhoeff-van Gieson stain. (×200; reduced ½.)

or arteriolitis. The changes in the pulmonary vessels were also arbitrarily graded from zero to four-plus on the same basis as the alveolar changes. The vascular changes are shown in Figs. 4 to 8.

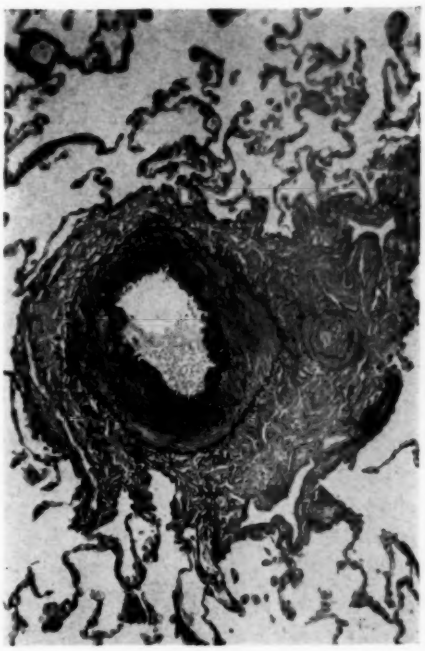

Fig. 8.—Medium-sized artery with fragmentation of elastic lamina; interstitial fibrosis of alveolar walls. Verhoeff-van Gieson stain. (×200; reduced ¼.)

Table I summarizes the clinical, laboratory, and pathologic findings.

It can be seen that the most marked alveolar and vascular changes tended to occur in the older patients who had had their disease for longer periods, in patients with advanced disease, right ventricular hypertrophy, radiologic evidence of pulmonary fibrosis or hemosiderosis, high pulmonary artery pressure, and increased total pulmonary and pulmonary arteriolar resistances. There were noteworthy exceptions to all clinical and laboratory features, none of which consistently correlated with the pathologic findings.

DISCUSSION

The postoperative period has been inadequate for evaluation in the majority of our patients. We have not had an opportunity to perform repeat biopsies and all of the patients are still alive. Only five have been restudied by cardiac catheterization 6 or more months postoperative. Patient No. 10 showed no significant change but her valvulotomy was not considered satisfactory due to technical difficulties. Patients 4 and 12 showed significant reductions in pulmonary pressures and resistances but their pulmonary changes were graded only zero to two-plus. In these patients the increased pulmonary resistance must have been due to vasoconstrictor activity or the slight medial hypertrophy found in one patient. Patient No. 9 has shown marked improvement in every respect.

TABLE I

PATIENT	AGE	SEX	DURATION OF SYMPTOMS	CLINICAL CLASSIFICATION	EKG	X-RAY	"PC" PRESSURE	PA PRESSURE	ARTERIOLAR RESISTANCE	PULMONARY RESISTANCE	ALVEOLAR CHANGES	VESSEL CHANGES
1	28	F	5 yr.	III	N	N	—	53/22	—	583	±	−
2	49	F	4 yr.	II	N	N	15/6	40/23	595	857	+	+
3	59	F	20 yr.	IV	N	N	20/15	40/20	459	1199	4+	4+
4	30	F	5 yr.	III	N	N	12/2 —	42/20 25/7	505 —	620 384	2+ (6 mo. posto	+ perative)
5	30	M	1 yr.	II	N	N	15/7	23/6	49	355	+	−
6	42	F	6 yr.	II	N	N	45/23	58/30	61	1484	2+	2+
7	40	F	6 mo.	III	N	H	23/17	46/18	751	1540	4+	4+
8	39	F	3 yr.	IV	RVH	H	31/12	116/37	967	1354	2+	2+
9	29	F	7 yr.	III	RVH	H	26/16 22/10	90/33 54/24	344 398	545 676	3+ (8 mo. posto	3+ perative)
10	37	F	3 yr.	III	N	H	45/15 33/12	53/18 40/16	72 —	429 —	2+ (6 mo. posto	2+ perative)
11	29	F	6 mo.	II	N	N	22/12 8/5	34/14 23/9	126 166	451 309	+ (7 mo. posto	− perative)
12	24	F	6 yr.	III	N	N	40/18 16/10	58/26 40/15	238 209	752 438	2+ (7 mo. posto	− perative)
13	38	F	18 mo.	IV	RVH	H	—	110/38	—	2740	4+	3+
14	33	F	4 yr.	III	RVH	H	—	96/37	—	2169	2+	2+
15	29	F	2 yr.	III	RVH	N	59/33	87/36	432	1907	4+	3+

N: Normal; RVH: Right ventricular hypertrophy; H: Hemosiderosis and fibrosis.

She is asymptomatic on unlimited activity which includes mountain hiking and skiing. Cardiac catheterization 8 months postoperative showed a slight drop in her "capillary" pressure, a marked drop in her pulmonary pressure but a slight increase in pulmonary resistances. Her chest roentgenogram shows a marked decrease in the pulmonary fibrosis and hemosiderosis. Her heart size has decreased slightly and while her electrocardiogram is still abnormal, the evidence of right ventricular hypertrophy is less marked. Her lung biopsy showed three-plus alveolar and artery changes. The latter consisted of thickening of the walls of the arterioles and medium-sized arteries; no intimal fibrosis was noted. None of our preoperative studies or the lung biopsy predicted such an excellent result.

Our clinical impression has been that patients with far advanced pulmonary changes show less benefit from mitral valvulotomy, but we have had noteworthy exceptions. Patients No. 7 and 13 have shown very gratifying improvement while others with less advanced pulmonary changes have shown less benefit. This impression plus our experience with patient No. 9 adds support to the conclusions of Edwards and associates[8] who believe that the pathologic changes in the pulmonary vessels cannot be used as a reliable index for predicting whether or not a satisfactory functional response would result from valvulotomy. Patients with predominantly medial hypertrophy can be expected to benefit from valvulotomy while those with predominant intimal fibrosis or medial scarring should derive less benefit from an operation to relieve the obstruction at a narrowed mitral valve. Unfortunately we do not have a reliable index for predicting the state of the pulmonary vessels prior to operation. Nor do the pulmonary vessels as found on lung biopsy necessarily foretell the functional result. Until we attain reliable criteria, continued attempts to develop an operation to relieve severe mitral stenosis seems justifiable, even if preoperative studies suggest advanced pulmonary vessel changes.

SUMMARY

1. A pathologic study of lung biopsies from fifteen cases of well-established mitral stenosis was made with the purpose of correlation of the alveolar and pulmonary vessel changes with the clinical and laboratory findings. A control group of ten autopsy cases without cardiac or pulmonary disease was also studied.

2. The changes in the alveolar walls consisted of capillary dilatation, thickening of the capillary basement membrane, increase in the interstitial tissue, pericapillary edema, and a transition to cuboidal epithelium.

3. The lesions in the pulmonary vessels consisted of intimal thickening, medial hypertrophy, and scarring with narrowed lumens.

4. Such changes were more commonly found in older patients with more advanced disease, in those with roentenographic evidence of pulmonary fibrosis or hemosiderosis, electrocardiographic evidence of right ventricular hypertrophy, high pulmonary artery pressures, and increased pulmonary and pulmonary arteriolar resistance. Pulmonary vessel changes could not be consistently predicted by any clinical or laboratory finding.

5. Patients with marked pulmonary changes tend to derive less benefit from mitral valvulotomy, but there are noteworthy exceptions.

6. No single feature or group of features is completely reliable in determining the degree of pulmonary changes present prior to operation nor do the pulmonary changes as determined by lung biopsy necessarily predict the degree of benefit to be obtained from valvulotomy.

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RISK OF THROMBOEMBOLIC COMPLICATIONS FROM CORTISONE THERAPY

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AN increased coagulability of the blood has been reported in the hyperadrenal state induced by the therapeutic administration of corticotropin (ACTH) and cortisone.[1-4] Cosgriff and associates,[1] after having encountered a number of thromboembolic complications during the course of such therapy, considered the possibility that these agents may promote a thrombotic tendency by producing a state of hypercoagulability of the blood. Their suspicions appeared to be confirmed by their subsequent discovery of changes in the venous clotting time and the heparin-retarded venous clotting time among patients receiving these hormones. In independent studies, Smith and co-workers[2] observed similar alterations in the coagulability of the blood but, since these changes were by no means uniform from patient to patient, acknowledged that their observations did not allow any broad conclusions. More recently, Cosgriff[4] has recorded the occurrence of forty episodes of thromboembolic disease in 28 out of 700 patients treated with ACTH or cortisone. While recognizing that these complications may have been more closely related to the underlying disease states than to the hormonal agents employed, Cosgriff asserts that thromboembolic phenomena should be considered as one of the serious complications of corticotropin and cortisone therapy.

Since thrombotic complications are more prone to develop in persons with underlying vascular abnormalities or with a history of previous thromboembolic disease, it would appear that the employment of ACTH or cortisone in such thrombophilic individuals demands utmost circumspection. For these cases, Cosgriff[4] has suggested the use of prophylactic anticoagulant therapy during and for several weeks following the course of hormonal therapy. Without clear knowledge of the actual risk involved in the use of ACTH or cortisone, however, it is difficult to establish a basis for preventive treatment which is itself responsible for significant morbidity and mortality. The administration of Dicumarol has been identified as one of the leading causes of death due to drugs.[5] Moreover, from available evidence it cannot be stated unequivocally that the risk of thromboembolic phenomena from ACTH and cortisone presents a more serious threat to recovery than the risk of hemorrhagic complications from Dicumarol. Under

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certain circumstances the small benefit to be derived from anticoagulant drugs may be completely vitiated by their hazards. In acute myocardial infarction, for example, the incidence of thromboembolism is so low among the milder ("good risk") cases, that the employment of Dicumarol prophylactically in such instances must be regarded as an unwarranted procedure.[6] Similarly, in order to evaluate the need for anticoagulant therapy in patients with underlying vascular disease who are to receive ACTH or cortisone, an idea of the probable incidence of thrombotic phenomena attributable to these agents is necessary. With the widespread employment of ACTH and cortisone and their increasing field of usefulness, the physician will frequently be confronted with the problem of whether or not coexisting disease of the heart or blood vessels represents a contraindication to hormonal therapy. The purpose of this communication, therefore, is to record the authors' experience in eighty-six consecutive patients with serious vascular disease who received a course of cortisone in relatively large dosage.

MATERIAL

When cortisone first became available, the effect of the drug in six patients with angina pectoris was studied solely to determine its influence on coronary reserve. To accomplish this, the Master two-step test was performed at frequent intervals during a three-week course of cortisone. Subsequently, five additional

TABLE I. ANALYSIS OF CASES WITH VASCULAR DISEASE TREATED WITH CORTISONE

VASCULAR DISEASE	NO. PATIENTS	CONDITION TREATED	INITIAL DOSE MG. DAILY	DURATION OF THERAPY (DAYS)
Angina pectoris	6	None	200	21
Angina pectoris, coron. insufficiency	5	Bronchial asthma (2)	200	21, 23
		Sympathetic ophthal. (1)	200	101
		Exfoliative dermatitis (1)	300	48
		Histaminic cephal. (1)	300	22
Acute myocardial infarction	27	Atypical pneum. (2)	200	14, 15
		Shoulder-hand syn. (25)	200–300	21
Cerebrovasc. occlusion (hemiplegia)	34	Hemiplegia	200–300	21
Apoplectic stroke	12	Apoplectic stroke	250–300	21
Cong. heart failure	2	Acute bursitis	200	8, 10

cases of angina pectoris or coronary insufficiency received cortisone for various reasons; severe bronchial asthma was present in two instances, sympathetic ophthalmia in one, exfoliative dermatitis in one, and histaminic cephalalgia in one. There were twenty-seven patients with acute myocardial infarction in the total group; of this number two received cortisone as a heroic measure for atypical pneumonia unresponsive to antibiotics, while twenty-five received the drug for refractory shoulder-hand syndrome.[7] Marked cerebrovascular disease manifested

by hemiplegia was present in forty-six of the eighty-six patients in the series. In thirty-four hemiplegic patients cortisone was employed as an adjunct in rehabilitation[3] long after recovery from the apoplectic stroke, whereas, in the remaining twelve it was prescribed as treatment for the acute cerebrovascular accident[9] itself.

Chronic congestive heart failure was present in 2 patients in the series, both of whom received cortisone as treatment for acute bursitis. A history of previous episodes of congestive heart failure was obtained in twenty of the eighty-six patients. Marked obesity, varicosities in the lower extremities, and previous thrombophlebitis were coincidental findings in a significant number of the cases. Of the eighty-six patients, fourteen were confined at bed rest during the course of cortisone, sixty-one were semiambulatory and partially restricted, and eleven were engaged in normal activity. Twelve per cent of the entire group were female subjects. Ninety-one per cent were between the ages of 40 and 74 years, an age range in which clinical thrombotic complications are commonly encountered.

Administration of Medication.—In most instances 200 mg. of cortisone was administered orally in divided doses on each of the first two days with progressive diminution to a maintenance dose of 50 mg. daily through the third week. In several cases the drug was given parenterally in similar dosage. Eighteen patients received initial doses of 300 mg. daily. Three patients were continued on maintenance therapy for 4 to 14 weeks, while four were under treatment for only 2 weeks. All patients were placed on a low-salt diet with 3 Gm. of potassium chloride orally per day in divided doses. Serial serum sodium and potassium levels were not obtained.

RESULTS

No thromboembolic complications were encountered in this series during the course of cortisone therapy and for several weeks following its termination. There was no aggravation of symptoms attributable to the hormone in patients with angina pectoris and the levels of blood pressure in those with hypertensive disease were also uninfluenced by the drug. With the simple precautions taken, clinical symptoms of sodium retention were not encountered; even in the patients with chronic congestive heart failure usual measures effectively controlled edema.

COMMENT

In spite of evidence which indicates that cortisone may produce a state of hypercoagulability of the blood in some patients, the danger of thromboembolic complications from its use must, in the light of present findings, be regarded as relatively slight. Although all of the eighty-six patients in the present series had serious cardiovascular and/or cerebrovascular disease, no thrombotic episode was observed in any case during the course of hormonal therapy or in the subsequent posttreatment period. In these patients no specific measures were employed to prevent thromboses except for encouragement of active and passive motion and frequent change of position in bed. In the great majority of the

patients cortisone was prescribed as part of a program of physical rehabilitation so that exercise and activities of daily living were encouraged and commonly practiced. Although the value of such procedures in the prevention of thromboembolism should not be minimized, it seems apparent that the administration of cortisone does not constitute a sufficient threat clinically, even in patients with serious vascular disease, to interdict its use or to require anticoagulants prophylactically.

Cosgriff expressed the view that an apparent correlation exists between thromboembolic complications and the dosage of cortisone. In his series of cases exhibiting thromboembolism, however, only two patients received in excess of 100 mg. daily. In the present study, the initial dose was 200 mg. or more per day, a fact which, according to Cosgriff, should have heightened the tendency to thrombosis. The results of this investigation indicate not only the apparent rarity of thromboembolism due to cortisone but also the relative safety in administering this drug to patients with coexisting disease of the heart or blood vessels when ordinary precautions are taken and close supervision is maintained.

SUMMARY

An increased coagulability of the blood has been reported in the hyperadrenal state induced by the therapeutic administration of corticotropin (ACTH) and cortisone. This finding, as well as a seemingly high incidence of thromboembolism in patients receiving such treatment, has led some authors to consider the use of anticoagulants when serious vascular disease or thrombophilic tendencies are present in patients requiring hormonal therapy. Without clear knowledge of the actual risk involved in the use of ACTH or cortisone, however, clinical judgement as to the selection of cases for treatment and the need for preventive measures must remain clouded.

The present communication has recorded observations in eighty-six patients with advanced cardiovascular and/or cerebrovascular disease who received large dosages of cortisone in a course of therapy generally extending over a period of three weeks. In these patients no thromboembolic phenomena or other vascular complications were encountered during the administration of the drug or following its withdrawal. This experience seems to indicate that the theoretical danger of thrombotic complications from the use of cortisone is not clinically significant and that underlying disease of the heart or blood vessels need not preclude such therapy when proper supervision and simple precautions are instituted.

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THE ERYTHROCYTE SEDIMENTATION RATE IN HEMOCONCENTRATION ASSOCIATED WITH ACUTE MYOCARDIAL INFARCTION

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WITH THE TECHNICAL ASSISTANCE OF ALICE EINHORN, B.S.

WHILE an elevated erythrocyte sedimentation rate (ESR) in patients with anemia does not necessarily indicate an inflammatory process, a normal value in the presence of hemoconcentration may fail to indicate even severe inflammatory activity. It is common practice to correct the ESR for anemia according to the hematocrit reading.[1,2] Although, on the other hand, the inverse relationship between the ESR and the hematocrit has been known[3-5] it has not been sufficiently emphasized that the ESR may be normal despite the presence of pronounced inflammatory manifestations when hemoconcentration appears.

In a study of fifty patients with acute myocardial infarction,[6] we observed that the ESR in some cases remained initially normal for an unusual length of time, despite the presence of various objective signs indicating a marked inflammatory reaction. These signs consisted of fever, leukocytosis, and elevation of the plasma fibrinogen level. It appeared that the hemoconcentration associated with the clinical picture of massive myocardial infarction and as reflected in a high hematocrit reading might prevent the ESR from attaining values corresponding with the degree of inflammatory intensity. On the other hand, the fibrinogen concentration always reflected the severity of the condition of these patients. Serial studies of the ESR, the hematocrit, and the fibrinogen levels were undertaken therefore in six patients with a clinical picture suggestive of massive myocardial infarction and showing definite evidence of hemoconcentration.

In addition, in vitro experiments were carried out in which increasing hematocrit readings were produced by successive removal of plasma. The ESR was then correlated with the respective hematocrit.

MATERIALS

A. In six out of fifty patients with acute myocardial infarction,[6] the ESR, the plasma fibrinogen concentration, as well as the hematocrit reading, were determined serially every other day over a period varying from one to seven weeks according to the duration of illness.

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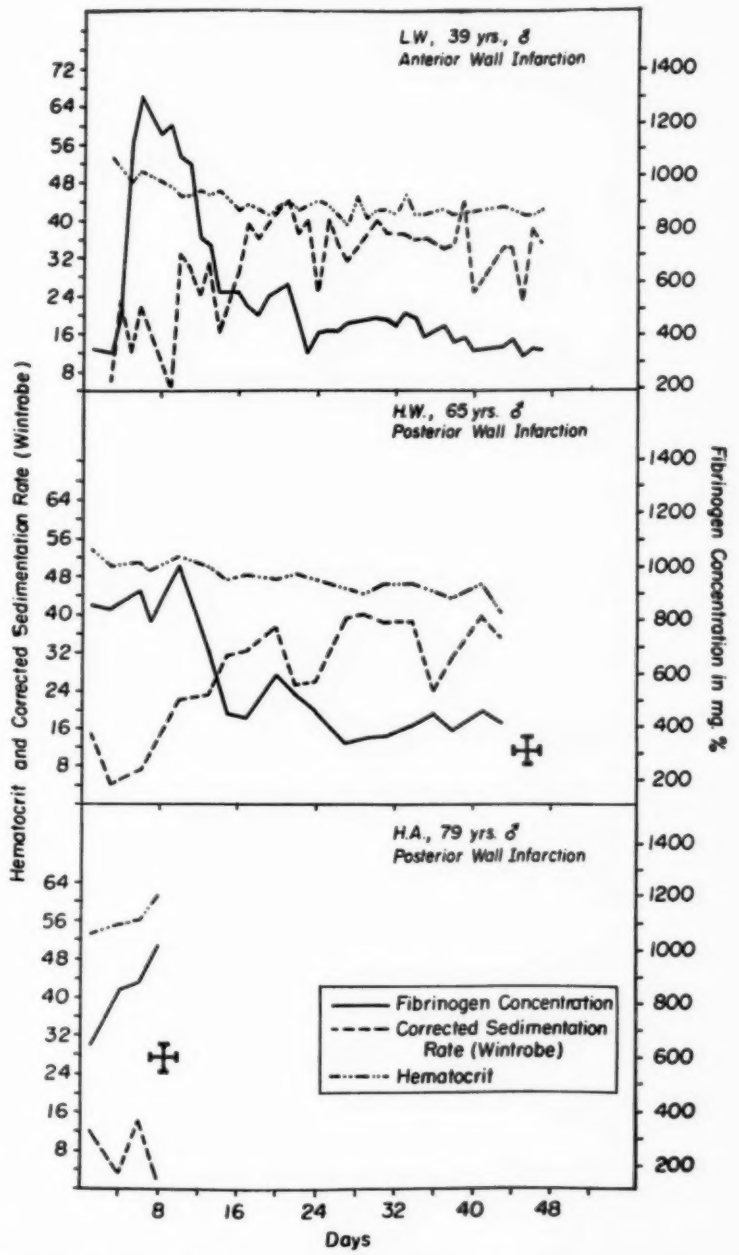

Fig. 1.—Comparative course of ESR, hematocrit, and fibrinogen in three representative cases of acute myocardial infarction. ESR remains normal as long as hematocrit exceeds 48.

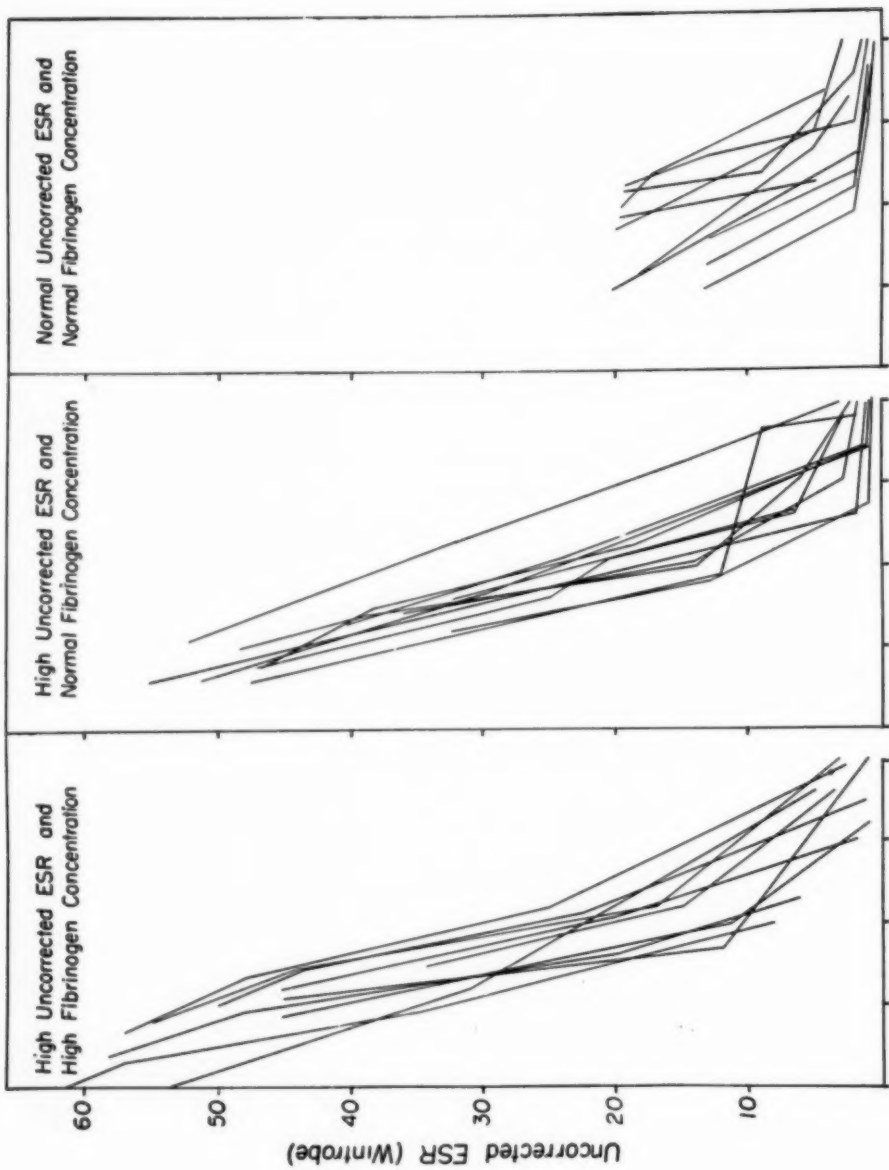

Fig. 2.—Correlation between ESR and hematocrit. Increasing hematocrit readings obtained in vitro by successive removal of supernatant plasma.

B. Venous blood was obtained from thirty patients divided into three groups of ten subjects each according to their ESR and fibrinogen concentration. Group 1 comprised ten patients with diabetic gangrene, acute rheumatoid arthritis, and acute rheumatic fever. The uncorrected ESR in these patients ranged from 34 mm. to 62 mm. per hour and the plasma fibrinogen level varied from 462 mg. to 750 mg. per cent.

Group 2 consisted of ten patients with urinary and upper respiratory infections whose uncorrected ESR ranged from 32 to 55 mm. per hour while the plasma fibrinogen concentration was within normal limits varying from 246 to 408 mg. per cent.

Group 3 comprised ten subjects with a normal uncorrected ESR and a normal plasma fibrinogen concentration.

METHODS

A. In the clinical study of the six patients with myocardial infarction 10 c.c. of venous blood were drawn, of which 5 c.c. were placed in a B-D vacuum tube for the determination of the ESR and the hematocrit according to the Wintrobe-Landsberg method.[1] The remainder of the blood served to fill a graduated centrifuge tube to the 5 c.c. mark which contained 0.5 c.c. of 0.1 molar solution of sodium citrate. The plasma derived from this specimen was used for the clot density determination of fibrinogen previously described by us.[5]

B. For the in vitro experiments thirty specimens of 5 c.c. of venous blood were drawn and added to a B-D vacuum tube containing balanced oxalates. The ESR was determined according to the Wintrobe-Landsberg method,[1] and the hematocrit was established subsequently. The remainder of the blood was centrifuged for three minutes after which time 0.5 c.c. of the supernatant plasma was pipetted off and discarded. Plasma and red blood cells were resuspended by shaking the tube. A second ESR was then set up and the respective hematocrit reading was also obtained subsequently. The same procedure was repeated until a hematocrit of at least 54 was obtained.

RESULTS

A. Fig. 1 illustrates the comparative course of the ESR, the hematocrit reading, and the fibrinogen concentration in three out of the six patients with massive myocardial infarction. In all six cases the ESR was normal while the hematocrit fluctuated around 52, rising to higher levels when the hematocrit declined to values of 48 and less. During this acute phase of illness, prostration and hemoconcentration dominated the clinical picture which was associated with fever, leukocytosis and a very high plasma fibrinogen concentration. In all instances the maximum fibrinogen concentration during the first week more closely reflected the severity of the patient's condition.

B. As seen from Fig. 2 the initially elevated ESR returns to a normal value when the hematocrit reading is sufficiently increased. At a hematocrit of 54 only two specimens out of 30 disclosed an ESR which was slightly more than

normal. Upon further increase of the hematocrit to values in the vicinity of 60, all readings of the ESR were low and varied from 2 to 6 mm. per hour.

Although the patterns of the curves followed a general trend, they displayed considerable individual deviations so that it seemed impossible to deduce mathematically the ESR at a normal hematocrit from a given ESR associated with a high hematocrit reading.

DISCUSSION

The ESR is widely used as a simple laboratory procedure to indicate the presence of an inflammatory process. It is frequently applied in the clinical evaluation of acute myocardial infarction. In six out of fifty such cases studied by us, there was a complete absence of correlation between the ESR and the clinical picture during the first two weeks of illness. It has been noted previously by others that the ESR does not necessarily reflect the gravity of the clinical picture[3,8,9] and may even be normal when the myocardial infarction is massive.[10]

These findings were borne out by our clinical studies. It was observed that the ESR may be normal in the presence of pronounced signs of myocardial necrosis when the hematocrit was distinctly elevated as a consequence of hemoconcentration. On the other hand, it was also observed that the ESR became considerably accelerated when the hematocrit gradually declined, concomitantly with the clinical improvement. These observations were substantiated by our in vitro experiments in which the hematocrit reading was gradually increased by successive removal of plasma. The results observed in the patients as well as in vitro indicate that a high ESR can be reduced to normal values when the hematocrit is sufficiently raised.

Although the relationship between the ESR and the hematocrit appeared to follow a roughly similar pattern in each blood specimen, the resemblance was not great enough to allow a mathematical correlation, thus precluding a retrograde correction of the ESR toward a value associated with a normal hematocrit reading. These findings are well in keeping with the conclusion reached by Wintrobe[1,11] that the correction chart ". . . should not be used to 'correct' polycythemic blood to a normal level." Moreover, while the present study was in progress, additional evidence has been brought forth to ". . . cast serious doubt on the validity of any such correction charts."[12]

While the normal ESR thus does not seem to have any significance in the presence of hemoconcentration, the maximum fibrinogen concentration during the first week more closely reflects the severity of the clinical picture in spite of high hematocrit readings and is, therefore, a more reliable guide in the evaluation of the disease process than the ESR.

SUMMARY AND CONCLUSIONS

1. In six cases with signs suggestive of massive myocardial infarction and displaying hemoconcentration, the ESR remained normal for the first 10 to 14 days while the fibrinogen concentration paralleled the severity of the clinical status.

2. In vitro experiments corroborated the clinical observation of the inverse relationship between ESR and hematocrit.

3. In the presence of hemoconcentration, as evidenced by hematocrit readings between 50 and 54, the ESR seems to have no practical significance as an indicator of inflammatory activity.

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THE CLINICAL DIAGNOSIS OF BICUSPID AORTIC VALVE

A Study of Eighteen Cases

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THE condition of biscuspid aortic valve has been extensively studied from the anatomic point of view,[1-6] but a thorough clinical evaluation has not yet been recorded. For this reason, the diagnosis during the life of the patient can only be suggested, and this on rare occasions.

Anatomic investigations have established the existence of two types of bicuspid aortic valve: congenital and acquired. Embryologically the three sigmoid aortic valve leaflets do not have a common origin. The two anterior cusps originate from the dorsolateral extensions of the truncus septum, while the posterior leaflet springs from the intercalated dorsal swelling of the truncus arteriosus[7] (Fig. 1, a). When the latter process fails to evolve, a bicuspid aortic valve results by absence of the posterior leaflet. In this case the two existing leaflets are of equal size, and in neither of them is there a ridge. The coronary orifices are normal and correspond one to each leaflet, since there is no alteration in the development of the anterior leaflets[8] (Fig. 1, b).

Another type of congenital bicuspid aortic valve is seen as a result of failure of separation of the anterior cusps after the union of the lateral extensions of the truncus septum, thus giving origin to a single ventral leaflet, larger in size than the posterior. In this case the coronary ostia are both seen in the cusp of the combined anterior valve leaflet. In addition, it is usually possible to identify in this single anterior valve a midline ridge which embryologically represents the commissure which failed to develop between the two ventral cusps (Fig. 1, c).

This ridge is semicylindrical, with sharp parallel borders without fissures and its longitudinal axis corresponding to that of the aorta. In the microscopic examination it is seen that this ridge is not vascularized and that there are no evidences of an inflammatory process. Koletsky[3] describes another type of congenital bicuspid aorta in which there is a fusion of the right anterior with the posterior cusp.

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An acquired bicuspid aortic valve results from the almost complete fusion of two of any of the three valve leaflets along their commissures as the result of an inflammatory process, and this is generally of rheumatic fever origin.[3] Such a fusion gives rise to a ridge of irregular aspect without well-defined borders in which one can identify, microscopically, signs of inflammation. When one of the anterior cusps is fused with the posterior, the macroscopic identification of the acquired nature of the anomaly is facilitated by the presence of only one coronary artery ostium corresponding to the fused valve leaflet (Fig. 1, d).

Koletsky's series of eight acquired cases seems to us an outstanding fact that he has always found the fusion between both anterior cusps.

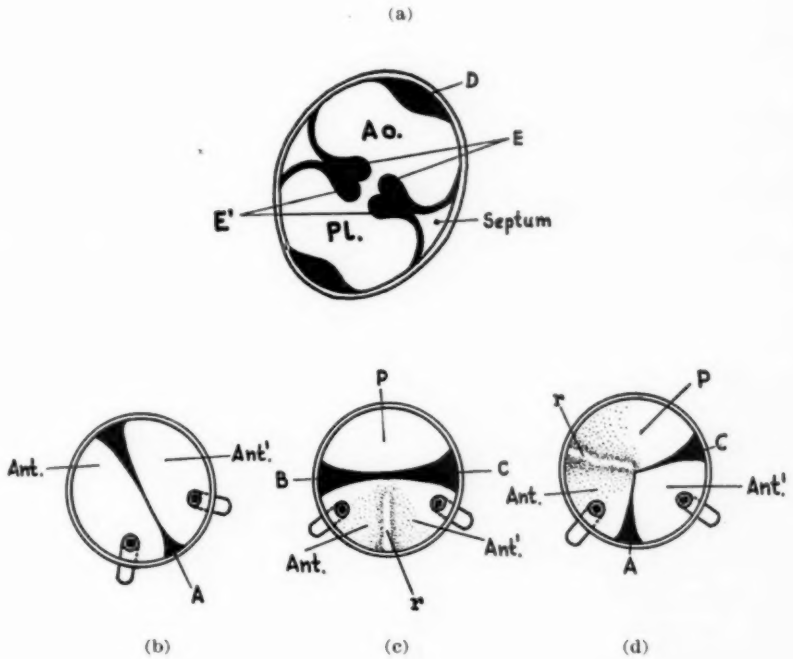


Fig. 1.—(a) Normal development of the aortic and pulmonary cusps: *Ao.*, aorta. *Pl.*, pulmonary artery. *E*, dorsolateral extensions of the truncus septum. *E'*, ventrolateral extensions of the truncus septum. *D*, intercalated dorsal swelling of the truncus arteriosus. *V*, intercalated ventral swelling of the truncus arteriosus. (b) Congenital bicuspid aortic valve originated by lack of development of the posterior leaflet. *A*, commissure. *Ant.*, right anterior cusp. *Ant'.*, left anterior cusp. (c) Congenital bicuspid aortic valve originated by fusion of the two anterior cusps. *r*, incomplete middle ridge. *B* and *C*, commissures. *P*, posterior cusp. (d) Acquired type of bicuspid aortic valve resulting from the partial destruction of commissure *B*. Note the location of the coronary ostia in relation with aortic cusps.

According to Koletsky the association of subacute bacterial endocarditis and bicuspid aortic valve, in the absence of another superimposed lesion, suggests that the valve anomaly is of congenital origin, while in the acquired forms it is possible to demonstrate the existence of rheumatic fever lesions. In the latter situation it is necessary to make a thorough study of the ridge in the valve leaflet

to recognize the true nature of the condition. The age of the patient and the coexistence of another congenital anomaly, particularly coarctation of the aorta, will help to resolve the problem.[1,2,6,9-11]

Up to the present time, few papers have been published on the clinical diagnosis of bicuspid aortic valve. Taussig[6] considers that this anomaly is beyond the clinical scope, that its importance lies in the possible association with another anomaly, and that it predisposes to subacute bacterial endocarditis.

The possibility of its existence is suggested by the presence of subacute bacterial endocarditis in a patient with no history of rheumatic fever and without clinical evidence of any other cardiovascular anomaly. Friedberg[12] holds the same point of view. From our observation on eighteen cases we have concluded that a clinical syndrome may be built, and through it the diagnosis of bicuspid aortic valve can be suspected.

MATERIAL AND METHODS

In 1,152 consecutive autopsies of cardiovascular cases from the Instituto Nacional de Cardiología of México, we found eighteen examples (1.56 per cent) of biscuspid aortic valve, and of these, eleven were classified as of congenital origin and seven as acquired, using these criteria. In outline form the cases had the following characteristics:

BICUSPID AORTIC VALVE
- *Acquired*
  - Rheumatic heart disease (one case with subacute bacterial endocarditis) — 6 cases
  - Syphilitic aortitis — 1 case
- *Congenital*
  - With subacute bacterial endocarditis — 8 cases
  - Without subacute bacterial endocarditis — 3 cases

Of the seven cases of acquired bicuspid aortic valve, six were associated with rheumatic heart disease with aortic valve lesions. In two of these cases, the lesion was fundamentally of stenotic type with calcification in one of them. Clinically, there were no signs of aortic insufficiency. In the other four cases, evidence of aortic regurgitation was found, both anatomically and clinically. In addition, in the majority of these cases, the mitral and tricuspid values were also damaged, and in one case there was an added subacute bacterial endocarditis.

Another case of acquired bicuspid aortic valve was associated with aortic syphilitic regurgitation without any evidence of rheumatic fever.

The eleven cases of congenital bicuspid aortic valve represent 21.1 per cent of fifty-two autopsied congenital cases. In this group, there were three in which the anomaly was due to the absence of the posterior valve and eight in which there was a single ventral valve leaflet. Eight cases had lesions of subacute bacterial endocarditis on the aortic valve, and all of these had signs of aortic insufficiency, both clinically and anatomically. One of these cases showed a high interventricular septal defect, so small that normal hemodynamics were not altered.

The other three cases did not have lesions of subacute bacterial endocarditis. One of these was associated with complicated syphilitic aortitis (aortic regurgita-

tion and aneurysm). This case was classified as of congenital origin after the histologic study of the ridge failed to demonstrate signs of inflammation, – in sharp contrast with the aortic wall, wherein abundant histologic evidence of syphilis was found. In addition the macroscopic appearance of the raphe was strongly suggestive of a congenital lesion. The second of these three cases was associated with coarctation of the aorta and showed clinical signs of aortic insufficiency. The third of these cases had an associated tetralogy of Fallot with a bicuspid aortic valve functionally sufficient.

We thus note that in the majority of the cases of acquired bicuspid aortic valve (five out of seven) there was a clinically important aortic insufficiency. Nevertheless we cannot link the anatomic finding and the clinical signs in this given situation since rheumatic heart diseases or syphilitic aortitis can produce per se, aortic insufficiency whether or not a bicuspid aortic valve has developed. It appears, then, that there are no reliable clinical signs of acquired bicuspid aortic valve in the presence of rheumatic heart disease or syphilitic aortitis. A similar conclusion may be drawn when these same processes are superimposed on a congenital bicuspid aortic valve, such as occurred in the previously mentioned case in which a bicuspid aortic valve of congenital origin was associated with syphilitic aortitis. One case like this has been previously reported by Richter.[13]

In most of the cases of bicuspid aortic valve of congenital origin, aortic insufficiency was also an important clinical finding. In general, these patients did not have a past history of either rheumatic fever or syphilis and on the other hand, there were signs and symptoms of active subacute bacterial endocarditis. We believe that the aortic insufficiency in these cases constitutes a strong diagnostic clue to suspect that subacute bacterial endocarditis was implanted on a congenital anomaly of the aortic valve, since there was no previous evidence of heart disease. For this reason, we were induced to think that an analysis of the secondary signs and symptoms in patients with aortic insufficiency might enable us to establish a symptom-complex, which would permit, in the majority of the cases, the diagnosis of bicuspid aortic valve of congenital origin. Based upon our experience obtained after the post-mortem study of seventeen cases, we were able to diagnose during life the last case of our series (proved by autopsy). We feel the relatively low incidence of congenital bicuspid aortic valve associated with other congenital cardiac anomalies observed in our series is related to the fact that most of our cases are over the second and third decades. This is in agreement with Koletsky's thought which explains that children with conplicated congenital anomalies usually have a short life span.

In the following analysis we did not include a case associated with tetralogy of Fallot without aortic insufficiency, since the valve leaflets were sufficient. In the same manner we excluded the case in which the congenital anomaly was associated with syphilitic aortitis, since the acquired lesion could explain by itself the aortic insufficiency.

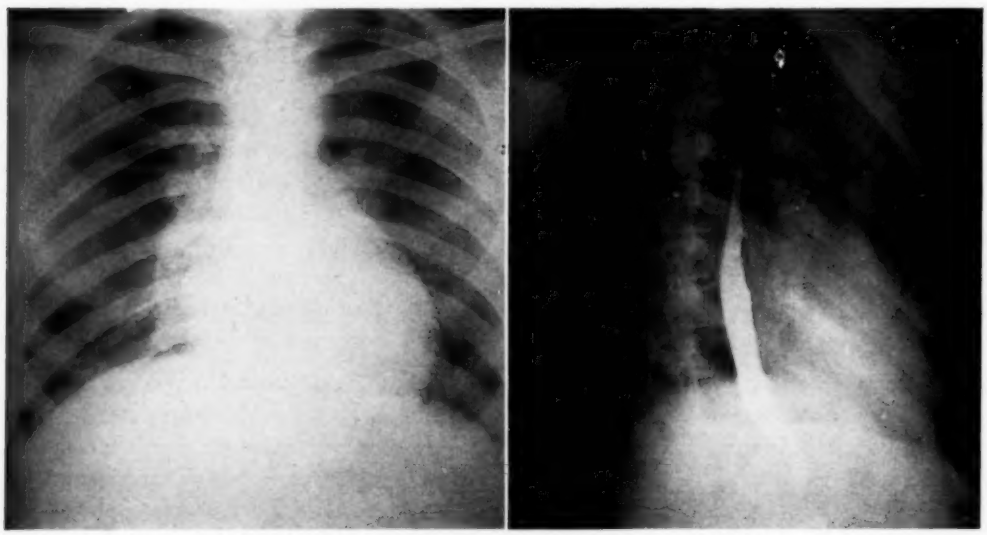
RESULTS

The results obtained in the nine cases of bicuspid aortic valve of congenital origin accompanied by aortic insufficiency may be summarized in the following manner:

Sex.—Of the nine cases, seven were men and two were women. Although this number of cases is not satistically significant, the ratio of 3.5 to 1 in favor of males found in our series approximates what has been reported previously.[5]

Age.—The age of our patients varies from twelve to thirty-eight years.

Clinical History.—As a rule the patients had been apparently well until the onset of the present illness and did not have a previous history of rheumatic fever or syphilis. In the clinical picture we noted three important features: syndrome of infection, cardiac failure, and aortic insufficiency.



A. *B.*

Fig. 2.—Roentgenogram of a 14-year-old male with congenital bicuspid aortic valve and subacute bacterial endocarditis in cardiac failure. Cardiomegaly Grade 2, predominantly of the left ventricle. The right chambers are slightly enlarged. Notice the absence of left atrium enlargement. The fluoroscopic dynamic was of aortic insufficiency.

Infection.—This was due to subacute bacterial endocarditis and appeared in eight of the cases. The only case excepted was that with coarctation of the aorta. We will make further comments on this case. Fever was generally of a significant degree, being more than 39°C. (102.2° F) and was the first sign in all the patients. There was a moderate or marked leukocytosis in all cases, reaching a count of 31,000 per cu. mm. in one case. The sedimentation rate of red blood cells was elevated in six of the eight cases (22 to 128 mm. in the first hour, Westergren). There were symptoms suspicious of pulmonary embolism in three patients (cough and bloody sputum). In one of the patients the clinical picture started with an embolic occlusion of the femoral artery. Only two patients showed hemoglobin in the urine; in one of these, large renal infarcts were found at autopsy, and in the other focal embolic nephritis was diagnosed microscopically. Blood cultures, often done for three consecutive days, and bone marrow cultures were made in seven of the eight patients with subacute bacterial endocarditis. In only two cases positive results were obtained, and in these Streptococcus viridans was isolated.

Cardiac Failure.—This was noted in seven of the nine cases. It was characterized by its severity and its rapid evolution. In the majority of the cases the picture of cardiac insufficiency was clinically more striking than the syndrome of infection, and in only one case was the infectious picture more dominant.

Aortic Insufficiency.—This was present in nine patients. In every case it was possible to identify a diastolic aortic murmur of moderate or marked intensity (Grade 2 to 4). There were peripheral signs of aortic regurgitation in all cases with high pulse pressure.

Likewise a systolic murmur was always heard, but its intensity was variable from Grade 1 to Grade 4. It was frequently transmitted to the neck vessels but was accompanied by a thrill in only three patients. These latter cases had subacute bacterial endocarditis and one of them showed calcification of the aortic valve. A systolic murmur was frequently described in the mitral area, and even a diastolic rumble was heard three times, but at autopsy the mitral valve was consistently normal.

Radiologic Characteristics.—In repeated radiologic examinations most of the patients were consistently judged to have cardiac enlargement of significant degree (Grade 2 to 3), predominantly of the left ventricle, with a fluroscopic picture of aortic insufficiency. In most of the cases an enlargement of the left auricle and the right chambers was also demonstrated, although the left atrium enlargement was moderate, never reaching the size that is seen in mitral cases (Fig. 2).

Electrocardiographic Characteristics.—Two of the nine cases had electrocardiographic tracings within normal limits. In the other seven, the tracings were suggestive of left ventricular strain, often associated with incomplete left bundle branch block. In some cases a right ventricular hypertrophy was also suggested, taking into account the relative deviation of $\hat{A}_{QRS}$ to the right, in the presence of signs of left ventricular strain (Fig. 3). In only two cases $\hat{A}_{QRS}$ deviated to the left ($-20°$ and $-30°$); in the remaining, $\hat{A}_{QRS}$ was between $+70°$ and $+100°$ ($+70°$, $+70°$, $+70°$, $+75°$, $+75°$, $+90°$ and $+100°$). The explanation of this finding is not easy. Nonetheless we have the impression that there are three probable contributing factors: the component of aortic stenosis that was found in all cases in greater or lesser proportion,[14] the presence of congestive cardiac failure, and finally the relatively short evolution of the aortic insufficiency.

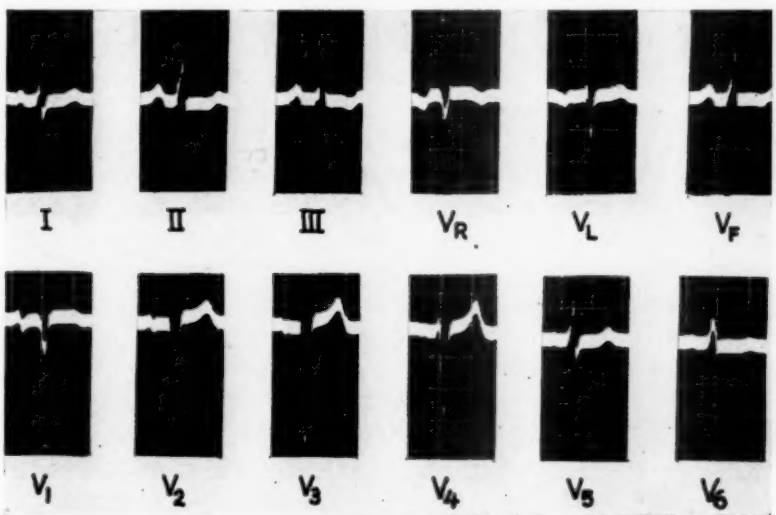


Fig. 3.—Electrocardiogram of a 26-year-old male with congenital bicuspid aortic valve and subacute bacterial endocarditis in cardiac failure. The tracing is suggestive of left ventricular strain, incomplete left bundle branch block; however, $\hat{A}_{QRS}$ is not deviated to the left ($+90°$).

It is proper to note that the electrocardiographic alterations and the radiographic findings noted are not peculiar to this condition; the same electrocardiographic signs, for example, could be found in the presence of a double aortic lesion of rheumatic origin, wherein there is a predominance of stenosis.

DISCUSSION

As we have already noted there are no clinical signs which, in the presence of rheumatic heart disease or syphilitic aortitis, would enable us to suspect the presence of an acquired bicuspid aortic valve. When these processes are added

to a bicuspid aortic valve of congenital origin in the same way, it would be impossible to suggest the diagnosis of the anomaly. In all the cases with rheumatic fever or with syphilis, the aortic insufficiency, if clinically existent, should be attributed to one of these diseases which in themselves can damage the valve and may or may not produce a bicuspid aortic valve. Therefore, acquired bicuspid aortic valve is a morphologic curiosity which lies beyond the clinical scope. If the case is that of an uncomplicated bicuspid aortic valve of congenital origin, the valve is sufficient, and the diagnosis of such anomaly is impossible because there is no clinical evidence of the condition.

However, it is of great interest to remark the high frequency with which subacute bacterial endocarditis is added to this congenital anomaly. This has been previously noted in the medical literature.[5,10] In our series, eight of eleven showed this complication (72.7 per cent). On the other hand it is probably significant that only one of seven cases of the acquired anomaly was complicated by subacute bacterial endocarditis. This would seem to indicate that in the cases of congenital origin the valve leaflets have a peculiar and marked tendency to harbor bacteria. As soon as subacute bacterial endocarditis is added to a bicuspid aortic valve of congenital origin and destroys the valve to a greater or lesser degree, aortic insufficiency appears clinically. This clinical picture, together with the presence of infection in the absence of rheumatic heart disease or syphilitic aortitis, enables us to suspect the presence of the anomaly of the valve. This suspicion may assume more diagnostic probabilities when we have other data which form a symptom complex to be described.

One case, with a congenital bicuspid valve and coarctation of the aorta, had clinical signs of aortic regurgitation even though the aortic valve revealed no evidence of subacute bacterial endocarditis. In this instance a possible explanation for the signs of aortic regurgitation lies in the presence of hypertension prior to the stenotic segment and the consequent dilatation of the valve ring, rendering the anomalous valve insufficient. Thus it has been suggested that in a case of coarctation of the aorta in which there are signs of aortic insufficiency (or of insufficiency and stenosis) the possibility of a bicuspid aortic valve must be considered, even in the absence of subacute bacterial endocarditis.[6] The other diagnostic possibility could be subaortic stenosis associated with the coarctation.[6]

In summary, what we consider the *clinical picture suggestive of congenital bicuspid aortic valve* is the following:

Young individuals, more commonly males, without rheumatism or syphilitic history, complain chiefly of sudden fever and in them for the first time cardiac failure with a rapidly progressive course ensues.

Physical examination shows signs of important aortic regurgitation. In many instances an apical diastolic murmur can be disclosed, but the clinician must keep in mind that this could be a functional murmur, therefore not necessarily indicative of mitral stenosis. Its presence has to be interpreted as for uncomplicated cases of patent ductus arteriosus,[15] and aortic regurgitation of syphilitic origin. Concerning this aspect of the diagnostic problem we would like to emphasize the value of the phonocardiographic study.

Clinical and laboratory findings may commonly lead to the diagnosis of subacute bacterial endocarditis. Occasionally, the presence of positive syphilitic

serologic tests raises the question of a syphilitic aortitis, although subacute bacterial endocarditis per se can give such positive reactions.[16]

The usual electrocardiographic findings are those of a left ventricular strain, although $\hat{A}_{QRS}$ is often found between $+70°$ and $+100°$. Roentgenographic examination shows very frequently left ventricular enlargement, seldom the left atrium is enlarged, but slightly.

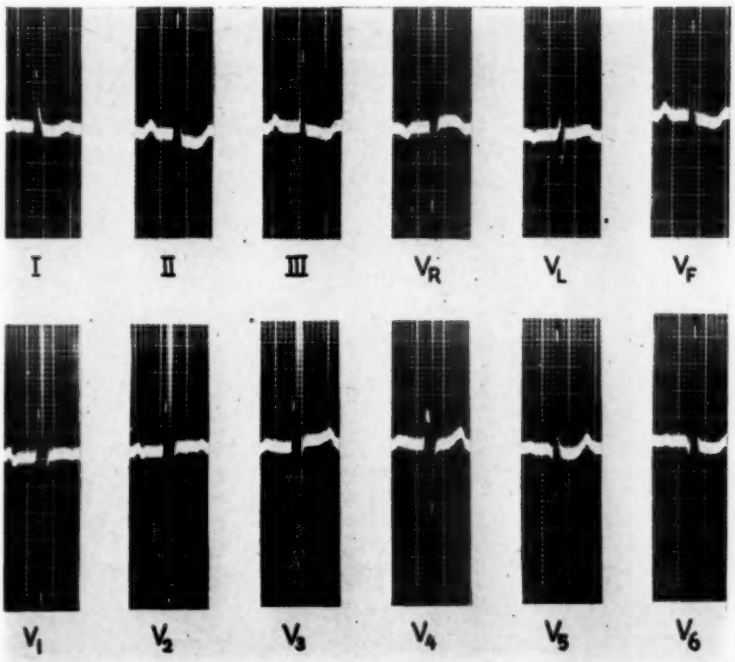


Fig. 4.—Electrocardiogram of a 27-year-old male with congenital biscuspid aortic valve and subacute bacterial endocarditis in cardiac failure (case reported). This tracing is characteristic of marked left ventricular hypertrophy, but $\hat{A}_{QRS}$ is + 70°.

Based upon this clinical picture it is possible to suspect the diagnosis of congenital bicuspid aortic valve. The following is the history of our last case in which we were able to prove at autopsy the diagnosis made during life:

The patient was a 27-year-old male admitted on May 26, 1953.

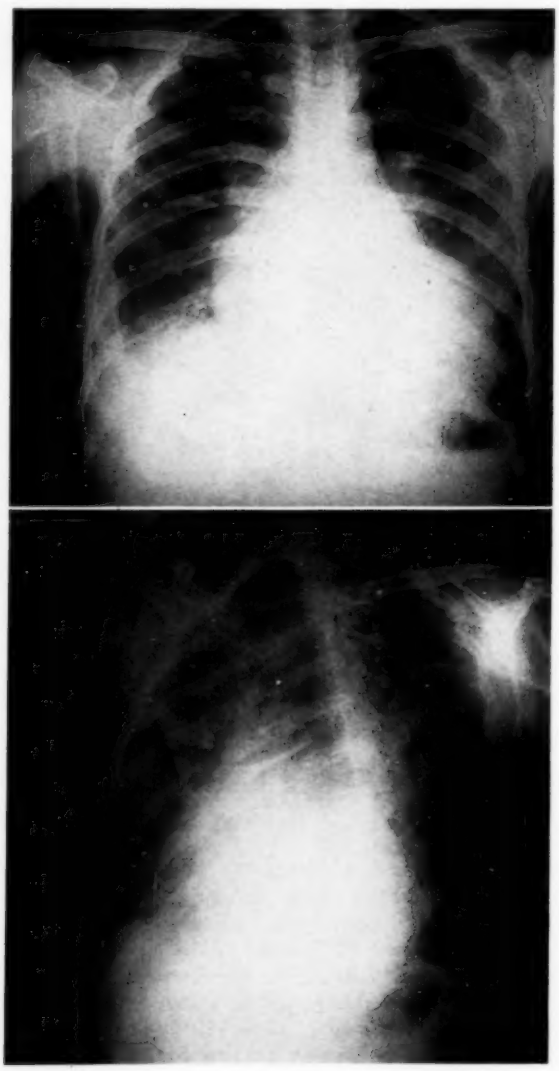
Two and one-half months before admission the patient noted a sudden sharp pain in the right groin with coldness of the right lower limb. The pain progressively subsided after 8 days. He also had fever, about 39°C. (102.2°F.), and complained of chills, general malaise and excessive sweating. On the second day the patient developed dyspnea of effort which in a week rapidly became continuous. During this period he suffered two attacks of acute pulmonary edema. One month prior to entry the patient noticed pitting edema of the lower extremities which disappeared after medical treatment. On admission he was complaining of continuous dyspnea, fever, and right upper quadrant dull pain, unrelated to meals.

His past history was negative for rheumatic fever and syphilis. He had played sports (football) without any discomfort.

Physical examination revealed an undernourished, polypneic, and diaphoretic patient, with a "café-au-lait" pallor and vigorous carotid pulsation. Along this artery it was possible to feel a systolic thrill and Corrigan's pulse. The apex was located at the sixth left intercostal space,

14.0 cm. from the midline. The apical impulse was increased and sustained. No thrills were felt over the precordial region. At the aortic area was heard a harsh Grade 2 systolic murmur, heard also on the neck vessels and the apex, and a blowing Grade 3 diastolic murmur transmitted to the apical area. A protodiastolic gallop rhythm was heard at the mesocardium. At the tricuspid area a soft Grade 2 systolic murmur reinforced in postinspiratory apnea could be identified. The liver was enlarged and tender. There was a Grade 2 splenomegaly. Blood pressure: 140/20 to 0 mm. Hg. Radial pulse had a Corrigan character. Pale clubbing of the fingers was present. The right popliteal posterior tibial and pedial pulse was absent.

A.



B.

Fig. 5.—Roentgenograms (posteroanterior and left oblique view) of the case reported showing pulmonary congestion, right pleural effusion, cardiomegaly Grade 3 with marked left ventricular enlargement. The right chambers are moderately enlarged. The left atrium does not compress the left bronchus. Fluoroscopic signs of aortic regurgitation were present.

The electrocardiographic findings (Fig. 4) were suggestive of marked left ventricular enlargement with $\hat{A}_{QRS} + 70°$ (combined ventricular strain?), first degree auriculoventricular block; digitalis action.

The roentgenographic study (Fig. 5) revealed pulmonary congestion; right pleural effusion; Grade 3 cardiomegaly, with marked left ventricular enlargement. The right chambers were moderately enlarged. The left atrium was only slightly enlarged. Fluoroscopic signs of aortic regurgitation were present.

Serial blood cultures rendered negative results. White blood cell counts showed a slight leukocytosis. Serologic tests for syphilis were positive.

Clinical course.—During his hospitalization the patient showed an increase of signs of cardiac failure with progressive downhill course, and on the eighteenth day died in spite of all pertinent therapy.

COMMENTS

The diagnosis of subacute bacterial endocarditis superimposed on a congenital biscuspid aortic valve was suspected by one of us (R. C.) from the beginning, based upon the clinical criteria established by our previous observations on the seventeen cases undiagnosed during life. The clinical history of this case represents the classical picture that has to be expected to suggest the possibility of the

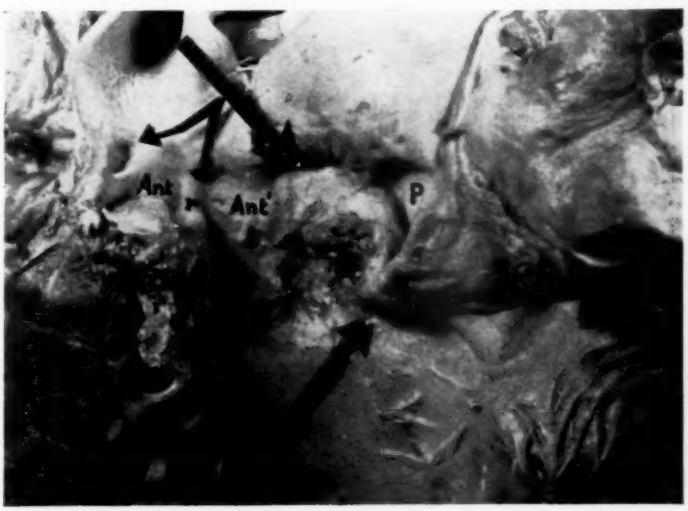


Fig. 6.—Photograph of the post-mortem specimen of the case reported. Congenital bicuspid aortic valve with superimposed subacute bacterial endocarditis. The anterior valve is formed by the fusion of the right (Ant.) and left (Ant.') anterior leaflets. The raphe (r) does not reach the free edge of the cusp. At either side of the raphe the coronary ostia are indicated. *P*, posterior cusp. The lower arrow shows the small interventricular septal defect.

congenital anomaly. The past history was negative for rheumatic fever and syphilis; the sudden appearance of severe and progressive cardiac failure preceded by a picture of an infectious process and arterial embolization (femoral) in a previously healthy young man, with signs of aortic regurgitation at the time of examination allowed one to think that a congenital bicuspid aortic valve with a

superimposed subacute bacterial endocarditis could explain the whole clinical picture. The admission diagnosis was reinforced by roetgenographic findings of left ventricular enlargement with only slight left atrial enlargement, in agreement with the electrocardiographic examination, although there was not left-axis deviation.

The pertinent *pathologic findings*, which confirmed the clinical diagnosis, are described below. Signs of a generalized infectious process and heart failure were present. The right femoral artery was found occluded by a thrombus. The pericardial sac contained about 50 c.c. of clear straw-colored fluid. The heart appeared enlarged in toto, with a marked preponderance of the left ventricle, and weighed 570 grams. The right atrium was moderately enlarged. The triscuspid circumference measured 115 mm.; the anterior and septal leaflets of this valve occluding partially the upper part of a congenital interventricular defect, 4 mm. in diameter, located in the highest and medial region of the septum. The left atrium was slightly enlarged. The mitral circumference measured 95 mm., and the valve was grossly normal. The aortic valve (Fig. 6) was formed by two cusps only: one large, anterior, representing the fusion of the two normal anterior leaflets, and the other small located posteriorly. The coronary ostia were found normally placed, both inside the fused anterior cusp. This leaflet was markedly deformed and stenotic with the presence of multiple vegetations, partially calcified. It also revealed, near the central portion, a large ulceration of about 5 mm. in diameter, which made the cusp insufficient. On the middle of the arterial surface of the cusp, a small ridge, with parallel borders, not reaching the free edge of the valve, was present. The posterior cusp was thick and retracted. Microscopic studies were confirmatory of the congenital nature of these malformations and excluded rheumatic fever and syphilis.

SUMMARY AND CONCLUSIONS

The authors studied, both clinically and pathologically, a series of eighteen patients with bicuspid aortic valve found among a total of 1,152 autopsied cases from the Instituto Nacional de Cardiología of México. Using Koletsky's criteria eleven cases were classified as congenital and seven as acquired. The congenital cases represent 21.1 per cent of all the congenital cardiac cases (52 cases) proved at autopsy. Eight of the eleven congenital bicuspid aortic valve cases (72.7 per cent) had superimposed subacute bacterial endocarditis. Of the remaining three cases, one was associated with coarctation of the aorta, another one with tetralogy of Fallot, and the last one with syphilitic aortitis.

It is emphasized that there are no clinical signs suggestive of an acquired or congenital bicuspid aortic valve in the presence of rheumatic and/or syphilitic heart disease.

The clinical analysis of the congenital cases confirms previous observations in the sense that this malformation, when present as an isolated finding does not give rise to hemodynamic disturbances and consequently produces no clinical signs.

Nevertheless, as most of our congenital cases had associated subacute bacterial endocarditis (an exceptional coincidence in the acquired type), which produced an insufficiency of the valve, classical signs of aortic regurgitation were present. These clinical signs in combination with those of the infectious process, in the absence of rheumatic or syphilitic heart disease, allow one to suspect the presence of the anomaly, especially if the patient is a young male whose clinical picture starts with high fever closely followed by severe and rapidly progressive cardiac failure.

The clinician must keep in mind that in this syndrome, as in cases of patent ductus arteriosus and of aortic regurgitation due to some other etiology, apical diastolic phenomena can be heard in the absence of a mitral lesion.

Roentgenographic examination usually reveals enlargement of all cardiac chambers, but there are two striking characteristics: the predominant enlargement of the left ventricle and slight enlargement of the left auricle.

Although the electrocardiogram shows signs of left ventricular strain, $\hat{A}_{QRS}$ is frequently found beyond +70 (an attempt has been made to explain this fact).

In the presence of coarctation of the aorta accompanied by signs of aortic regurgitation the diagnosis of an associated aortic bicuspid valve must be suspected.

The authors report a case of congenital bicuspid aortic valve, complicated with subacute bacterial endocarditis, diagnosed during life using their personal criteria.

We are indebted to Dr. Fernando Cisneros and Dr. W. Proctor Harvey for their valuable criticism, and to Dr. Edward Murphy for help in the English translation.

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COR TRIATRIATUM: A RARE MALFORMATION OF THE HEART, PROBABLY AMENABLE TO SURGERY

Report of a Case, With Review of Literature

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THE term cor triatriatum has been applied to a congenital malformation of the heart, in which a transverse septum is stretching across the left atrium, separating the opening of the pulmonary veins from the mitral orifice. The condition seems to be extremely rare, and in the few cases reported the diagnosis has never been suggested during life. With the rapid development of cardiac surgery, however, an effective treatment of this generally serious disorder now appears to be within the scope, and the possibility of an in-vivo diagnosis also in these rare cases may be of interest. In the following, the literature has been reviewed, and a further case is added, in which a mitral disease was suggested from clinical and physiological studies, and an explorative cardiotomy was performed, revealing a normal mitral valve.

CASE REPORT

A 29-year-old woman was admitted to the hospital in September, 1951, for mitral stenosis.

Past History.—Her development had been normal, but probably, she had had an attack of acute rheumatic fever during early childhood. From about 8 years of age she suffered from a moderate exertional dyspnea and was said to be slightly cyanotic after exercise.

She had been hospitalized twice before, in 1937 and in 1946. On both occasions no definite murmur could be heard, and roentgenograms showed the heart to be of normal size. In 1946 a prominent second left arch was reported, and marked congestion was seen in the lungs, together with signs of a previous pleurisy. Tubercle bacilli could not be cultured from the gastric lavage. In the electrocardiogram, in 1946, a right-axis deviation was present, with an inverted T wave in Lead III, but normal T in Leads I and II, and normal P waves.

In 1946, she went through a pregnancy and birth without complications, but after the delivery her condition deteriorated. Exertional dyspnea partly incapacitated the patient, who was unable to manage the more heavy domestic work, and she could walk only a hundred yards or upstairs to the first floor without stopping. She suffered from recurrent infections of the respiratory tract, and on several occasions she had small hemoptyses. Paroxysmal dyspnea or acute pulmonary edema had never been present, nor had any signs of right-sided congestive failure, and there was no history of peripheral embolisms.

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Physical Examination.—Height, 154 cm.; weight, 43.8 kilograms. The patient was not dyspneic at rest, but a slight cyanosis of the lips and cheeks was perceptible. Heart stethoscopy and phonocardiography failed to reveal any cardiac murmur. The first heart sound was normal at the apex, the second pulmonary sound was accentuated and probably reduplicated, but there was no true "mitral opening snap." Some crepitations were audible over the bases of the lungs. The liver was not palpable, and no peripheral edema could be demonstrated.

Laboratory Data.—Blood pressure was measured between 95/50 and 120/70 mm. Hg. Hemoglobin was between 80 and 90 per cent. The urine contained nothing abnormal, and blood urea was normal. The vital capacity of the lungs was greatly reduced (maximum 1.6 liters).

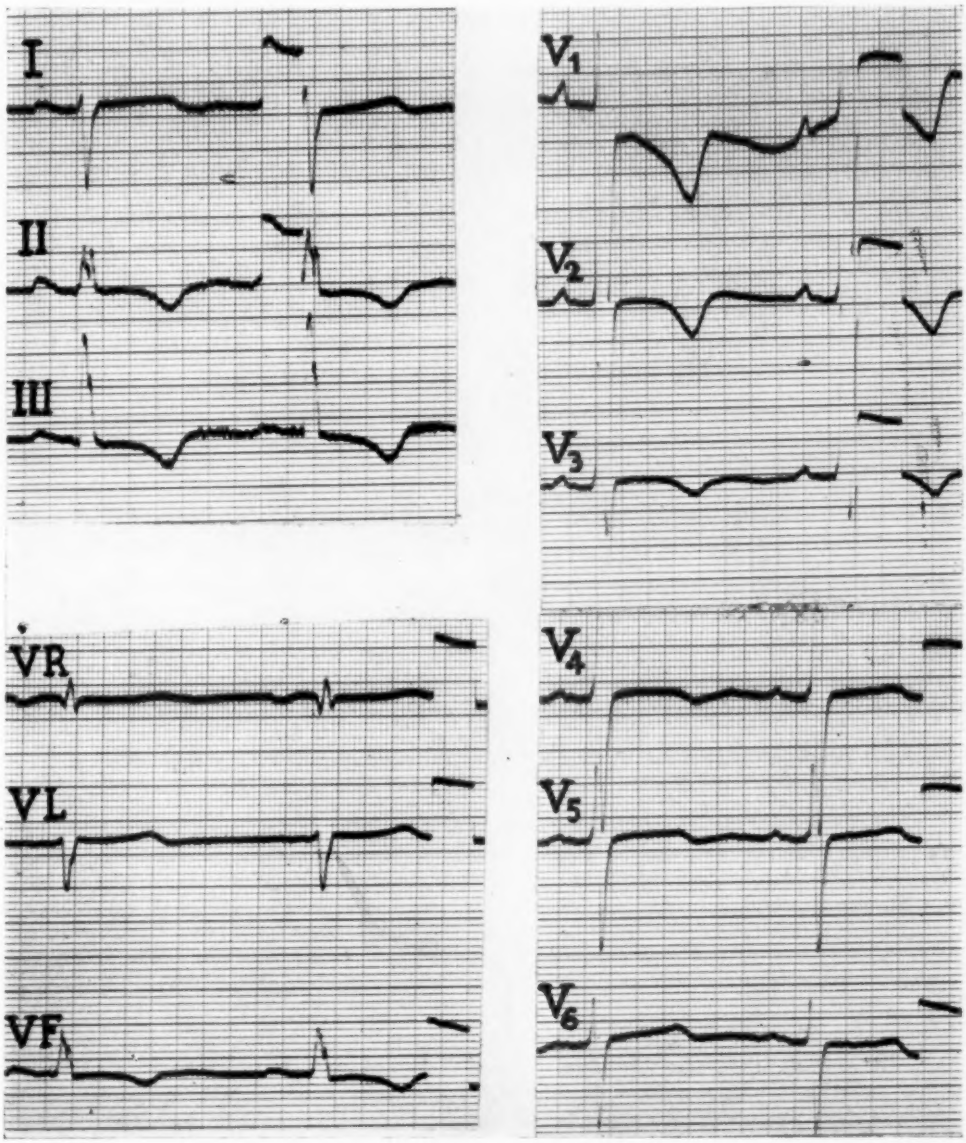
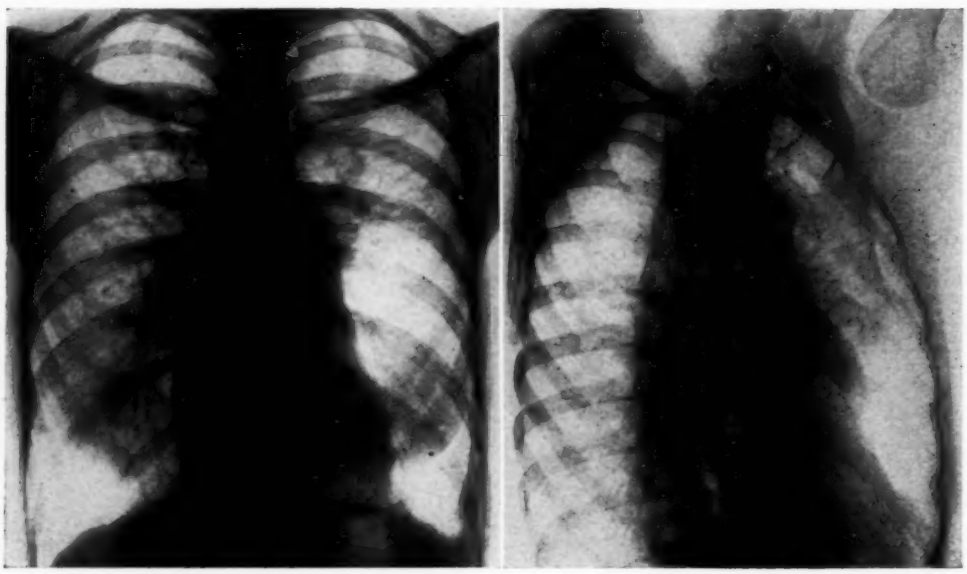


Fig. 1.—Electrocardiogram, showing a marked right ventricular hypertrophy and "strain" (Test: 1 mv.).

Electrocardiogram (Fig. 1): Sinus rhythm with normal P waves. Pronounced right-axis deviation in the standard leads ($\angle \alpha$ between $+130°$ and $+140°$) with T inversion in Leads II and III, and in the precordial leads, signs of right ventricular hypertrophy.

Roentgenogram (Fig. 2, *A* and *B*): The heart was of normal size. (Cardiothoracic ratio, 13:26.5. Heart volume, 550 c.c. per sq.m. body-surface area, using the method of Liljestrand and associates[1].) The left atrium was not found to be enlarged, nor was any of the other heart chambers. Only the pulmonary arch was markedly prominent, and there were highly increased hilar markings and pronounced pulmonary congestion, except for the left lower lobe which was emphysematous and showed signs of a previous pleurisy. *Bronchography* on the left side confirmed the presence of a localized emphysema, but otherwise revealed no abnormalities of the bronchial tree.



A. *B.*

Fig. 2.—*A*, Roentgenogram of chest, anteroposterior view. Heart of normal size, but with a distinct prominence of the second left arch and increased hilar markings. In the lungs signs of congestion and a localized emphysema of the left lower lobe. *B*, Roentgenogram of chest, right anterior oblique view with barium-outlined esophagus. No enlargement of the left atrium.

Heart Catheterization.—Pressures were recorded by means of the capacitance manometer elaborated by Hansen.[2] The percentage oxygen saturation of the blood samples was determined with the hemoreflectometer of Brinkman and Zylstra,[3] the oxygen capacity by van Slyke analysis. As will appear from Table I, an excessive pulmonary hypertension was present with a moderate further increase during four minutes' light exercise. The "pulmonary capillary pressure," too, was found to be very high, but an atrial curve could not be recorded in spite of attempts with the catheter at different places (Fig. 3). In the right atrium the level and form of the pressure curve were normal. The cardiac output at rest, as determined by the Fick method, was not decreased. During exercise, the oxygen consumption was not measured, but the oxygen saturation of mixed venous blood was unchanged. The blood samples showed no evidence of any left-to-right shunt, and the arterial oxygen saturation was normal and did not change during exercise (oximeter test).

From these findings the diagnosis was still obscure. The absence of any shunt excluded an Eisenmenger complex, or any other common congenital lesion, known to be able to produce a pulmonary hypertension (*e.g.*, cases with increased pulmonary flow). Theoretically, the lung lesions shown on the roentgenogram might be the cause of a pulmonary hypertension with a consequent strain on the right ventricle (chronic cor pulmonale), but the other findings did not

agree very well with this diagnosis. Moreover, the "pulmonary capillary pressure" has always been found to be normal in the conditions mentioned. According to all experiences this pressure reading, if properly performed, would indicate a pressure increase also at the venous side of the lesser circuit. As evidence of left ventricular failure was entirely absent, the site of the lesion in our opinion had to be the mitral valve, even if no apical diastolic murmur and no left auricular enlargement were to be demonstrated. Consequently, as the patient was an invalid, we considered the best thing we could offer her to be a thoracotomy for an eventual mitral valvulotomy.

Thoracotomy was performed in the usual way through a posterolateral incision with resection of the fifth rib. The lower lobe of the left lung was emphysematous and adherent to the chest wall and to the diaphragm. The right ventricle was found to be hypertrophied, and the pulmonary artery was enormous. After opening the rather small left auricular appendage the mitral orifice

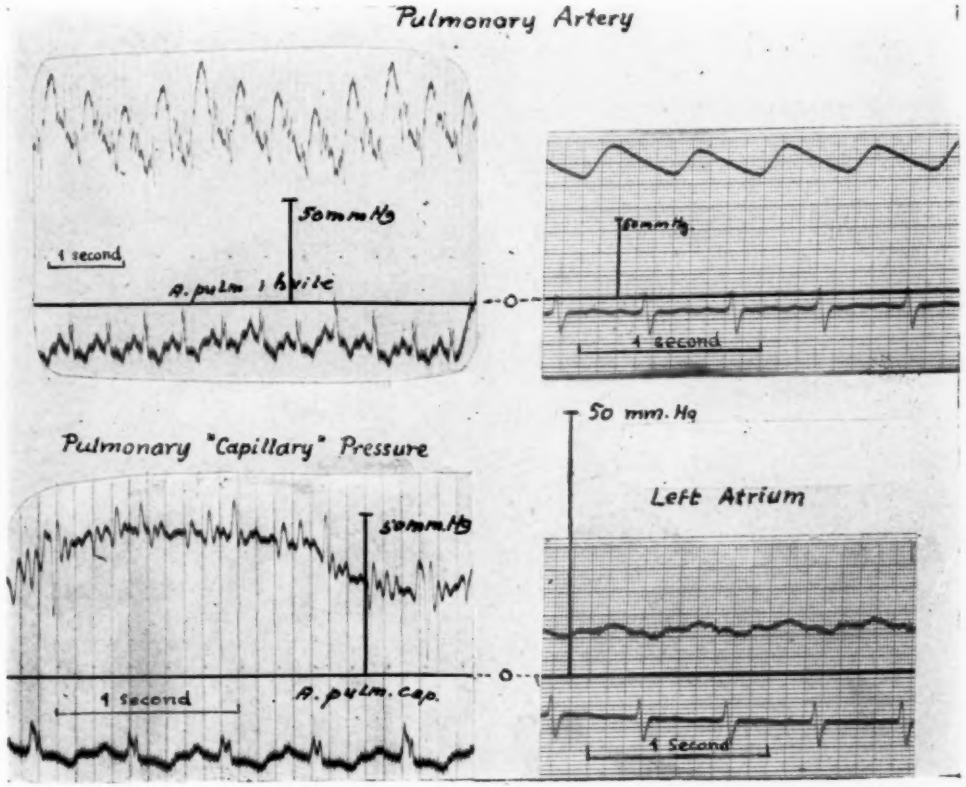


Fig. 3.—Pressure curves recorded on heart catheterization (left), and on direct heart puncture during thoracotomy seventeen days later (right). The pulmonary arterial curves are not very different, but there is a marked discrepancy between the high "pulmonary capillary pressure" and the normal pressure in the left atrium (distal to the septum). The rapid oscillations in the "pcv"-curve are probably due to catheter movements.

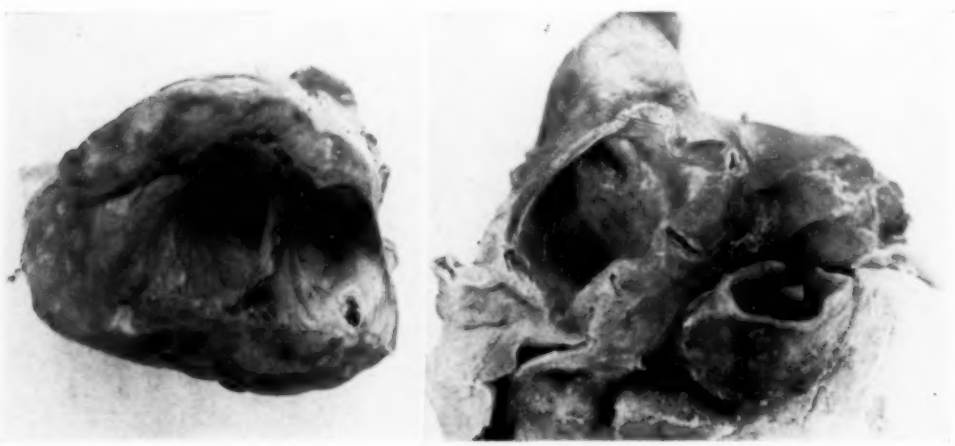
was explored. The valve was quite normal without any stenosis or regurgitation, and direct pressure measurement, using the technique described elsewhere,[4] revealed a normal pressure in the left atrium (Fig. 3 and Table I). After this we were not able to explain the high "pulmonary capillary pressure" reading during heart catheterization otherwise than being an artifact, and the thoracotomy was closed again.

The surgery was without complications, but afterwards the patient suffered from increasing dyspnea and cyanosis, and there was an abundant secretion of the respiratory tract, but aspiration was difficult. On the ninth day after surgery she died.

TABLE I. PHYSIOLOGIC FINDINGS

	HEART CATHETERIZATION (17 DAYS BEFORE THORACOTOMY)					DURING THORACOTOMY	
		PRESSURES (MM. HG)				PRESSURES (MM. HG)	
	OXYGEN SATURATION (%)	AT REST	DURING 4-MIN. EXERCISE	1 MIN. AFTER	18 MIN. AFTER	BEFORE AURICULOTOMY	AFTER AURICULOTOMY
Sup. vena cava	63						
Inf. vena cava	65						
Right atrium	60	m. 5			m. 4		
Right ventr.	60	95/5			105/4		
Pulm. artery	64–64	109/72–95/65	123/80	103/70	105/75	93/76	
Pulm. 'capill.'		m. 38–34					
Left atrium						m. 7	m. 8
Left ventr.						75/7	78/5
Femoral art.	95 (Oxygen capacity: 15.3 vol. %)						
Heart rate		118–108	140	116	110	130	136
Cardiac output $\frac{275}{14.5\text{-}9.8}$ = 5.9 liters/min.							

m. = mean pressure.



A. *B.*

Fig. 4.—*A*, Dissection of the left side of the heart, showing the anomalous septum with the irregular perforation (lower right). *B*, Left atrium opened from behind, directly upon the diaphragm (upper left).

*Post-mortem Examination.**—The heart weighed 425 grams. The right atrium was somewhat dilated with thromboses in the auricle. The foramen ovale was closed. The right ventricle was markedly hypertrophied, its wall measured 10 to 10.5 mm. The tricuspid and pulmonary valves were normal. In the greatly dilated pulmonary artery, especially in its smaller branches, pronounced atheromatous changes were present. The pulmonary veins on both sides were dilated,

*By Dr. V. Eskelund.

too, and rather thick-walled. They opened into a rounded cavity with a diameter of about 30 mm., situated at the posterior aspect of the heart, and separated by means of a diaphragm from the rest of the left atrium, which was of about the normal size. The only communication through this anomalous septum was an eccentric, irregular opening, measuring 5 to 7 mm. in diameter with scattered calcifications around its margin (Fig. 4, *A* and *B*). The surgical scar after the removal of the auricular appendage was closed, and situated between the septum and the mitral valve. The mitral and aortic valves and the left ventricle were normal, and so were the coronary vessels. In the wall of the thoracic and abdominal aorta several small patches of atheromatosis could be found.

The lungs showed evidence of chronic congestion and edema (brown induration). An acute bronchitis had been present, but no pneumonia or atelectasis. The pleura over the lower part of the left lung was covered by fibrinous and fibrous adhesions, fixing it firmly to the diaphragm. Histologic examination did not give any new information.

The liver and kidneys were also sites of chronic congestion. The spleen, adrenal glands, pancreas, genital organs, and the brain were normal.

DISCUSSION

The in-vivo findings all appear to be explained by the lesions found post mortem. The great stumbling block in the diagnostic considerations was the high "pulmonary capillary pressure", reflecting no atrial pressure curve. The absence of fluctuations in the "pcv"-curve does not necessarily compromise the reliability of this pressure reading as a measure of the mean pressure in the pulmonary veins, and it seems acceptable that the latter pressure really was at the level measured. In accordance with the principle of the formulas suggested by Gorlin and Gorlin[5] the area of the opening in the diaphragm may be calculated from the catheterization findings as $\frac{98.5}{44.9 \times \sqrt{36-5}} = 0.38$ sq. cm., which accords well with the post-mortem finding of an opening measuring 5 to 7 mm. in diameter. Thus, if these calculations are sound, a pulmonary venous hypertension of this degree (36 mm. Hg) could have been caused in the present case by the obstruction to the blood flow through the anomalous septum.

An additional great increase was found in pulmonary vascular resistance (about 680 dynes • sec. • $cm.^{-5}$), as it is frequently seen in analogous cases of mitral disease with pronounced pulmonary hypertension, but the nature of this vascular obstruction is not very well understood.

The clinical symptoms and signs may all be referred to the impeded blood discharge from the lungs with the subsequent pulmonary congestion and hypertension and right ventricular hypertrophy. Possibly, the complicating lung lesions to some extent may have contributed to the rather pronounced dyspnea and decreased vital capacity. The history and nature of these lung lesions were not elucidated.

Regarding the problem of an intravital diagnosis, it should be admitted that in this case it could have been made, if the digital exploration during thoracotomy had been extended to the posterior part of the atrium. Before operation it does not seem possible to obtain more than a suspicion of this diagnosis, and the actual problem, therefore, will be to select the suspected cases for explorative thoracotomy.

For this reason it has been attempted to summarize our present knowledge of this clearly uncommon anomaly, with special regard to the anatomic and clinicophysiologic features.

REVIEW OF LITERATURE

The presence of anomalous structures of congenital origin within the heart chambers is a rare occurrence. The few cases reported of cords or septa within the ventricles or the right atrium, which eventually may be of equal interest to the problem of a possible surgical relief, are left out of consideration here, and so is the equally rare and hemodynamically insignificant condition of a "double mitral orifice." Abbott in her analysis of 1,000 autopsies of congenital heart defects gave details of seventeen cases in which anomalous cordae (ten cases) or real septa (seven cases) in the left atrium were considered as the primary lesion, and moreover mentioned four cases with complicating other defects. Further casuistics of forty-five such cases have been found in the literature during the past century, references of which are made in a separate bibliography. A summary of the findings compared with some of Abbott's figures, is given in Table II.

As in Abbott's series it has been attempted to distinguish between cases in which only a cord or band was stretching along the walls or across the lumen of the atrium and cases with real septa (most commonly called cor triatriatum).

Abnormal *cords* or *bands* or *reticula* in the left atrium have been found in twenty-three of the cases listed. The one attachment of the cord was always at or in the neighborhood of the valve or limbus of the fossa ovalis, whereas the other end has been attached almost anywhere in the atrium or at the mitral valve, in one case (No. 28 in the bibliography) even continuing through the left ventricle up into the aorta. The thickness of the anomalous structure has varied, most often it was quite thin and threadlike, but also the presence of a broad band (Nos. 3 and 15), or of a more complicated reticular structure (Nos. 14 and 35) have been reported, thus being probable borderline cases to the real cor triatriatum. In nearly all cases no doubt has been aroused as to the congenital nature of the malformation. Associated congenital defects were described in only three of the patients, in whom the foramen ovale was patent (Nos. 3, 14, and 31, all adults).

One of patients (No. 29) died at the age of twenty-four from a streptococcal mitral endocarditis with a rapidly developing incompetence of the valve (confirmed on autopsy). In all the other cases in which further details are given the cause of death was insignificant, cardiac symptoms being entirely absent, and on post-mortem examination no effects on the heart and the circulation, contributable to the anomaly, could be demonstrated. Cardiac murmurs were only reported twice, viz., in the above case (No. 29) with mitral incompetence, showing an apical systolic murmur, and in No. 28 with the long cord through three heart chambers, in which a peculiar "to-and-fro" murmur was heard at the apex. According to Roessle[6] low-frequency murmurs of a peculiar character are frequently found in patients with aberrant cords in the left ventricle.

These few details agree fairly well with the findings of Abbott. Thus the conclusion must be that the presence of cords or even broader bands within the left atrium is probably always harmless, and not likely to cause any diagnostic problems.

TABLE II. SUMMARY OF SIXTY-TWO CASES FROM THE LITERATURE WITH ANOMALOUS CORDS OR SEPTA WITHIN THE LEFT ATRIUM

	CASUISTICS SUMMARIZED HERE		ABBOTT'S SERIES (1946)	
	CORDS	SEPTA	CORDS	SEPTA
Total number	23	22	7	10
Sex (male + female)	12 + 4	7 + 11	2 + 2	4 + 6
Age (given in)	15	18		
Mean	45	11	52	20
Range	1 — 67	0 — 70	35 — 84	0 — 48
Anatomy (detailed description in)	22	19		
Complicating anomalies				
Atrial septal defect	3	9	3	5
Abnormal number of pulm. veins		8		
Patent duct		3		
Tetralogy of Fallot		2		
Mitral endocarditis	1		1	1
Enlargement of heart	2*	11		
Right ventricle		16	1	9
Left atrium		5	—	6
Left ventricle		1**	1	2
Small left ventricle		10		
Congestion of lungs	1*	11		
Liver, kidney, etc.		7		
Clinical Symptoms and Signs (described in)	6	15		
Dyspnea		10		5
Paroxysmal dyspnea		4		1
Recurring bronchitis		2		
Hemoptyses		3		
Cyanosis (moderate to marked)		7		
Congestive failure		9		
Signs of pulmonary congestion	1*	5		
Heart Stethoscopy (reported in)	3	12		
Systolic murmur	1*	6	1	4
Diastolic murmur	—	2	—	1
Roentgenography (applied in)	1*	8		
Enlargement of heart	1	7		
Left atrium	1	—		
Cause of Death (suggested in)	11	15		
Still-born			—	1
Cardiac failure	—	14	1	2
Endocarditis	1*	—	1	—
Pneumonia	1	—	1	2
Other causes	9	1	1	2

*Refers to the case (29 in Bibliography) with mitral endocarditis and subsequent incompetence of the valve.

**Case 41 with a complicating hypertensive heart disease.

As would be expected, this will generally not be true when a real *septum* across the lumen of the atrium forms a coarse obstruction to the blood flow from the lungs. Only these cases seem to deserve the name double left atrium or cor triatriatum (Borst, 1905). Twenty-two of the cases from the literature have been referred to this category, and they have been summarized in detail in Table III.

TABLE III. NINETEEN CASES OF COR TRIATRIATUM (FROM THE LITERATURE)

CASE NO.*	POST-MORTEM FINDINGS							
	SIZE (DIAM.) OF PERFORATION IN DIAPHRAGM	ATR. SEPTAL DEFECT		PULMONARY VEINS (NO.)	COMPLICATIONS	HEART AND GREAT VESSELS	LUNGS	OTHER ORGANS
		POST. CHAMBER	ANT. CHAMBER					
2	10 × 17.5 mm.					Heart not enl., LA large, Right PV. dilat.	Congestion, edema	Generalized anasarca
4	?	Large		3	Tetralogy of Fallot	RV large		
5	Ant. slit				Tetralogy of Fallot, dextrocardia	RV large, LV rudimentary		
17	One large, several small			5 (3 rt.)		Otherwise normal!		
18	Post. slit: 10 mm.			5 (4 rt.)	Cyphoscoliosis	RV large, LV normal		
20	Several various-sized	1 mm.	+	3 (1 lt.)		RV large, Endarteritis of comm. carot. art.		
22	*intact!*	Small	Medium-sized	Both supp. to RA	No middle lobe of right lung	Heart enlarged, RV and RA large, LV small		
26	5 mm.					Heart enlarged, RV and LA large, LV and RA normal	Congestion, edema	Congestion of liver and spleen
30	Small	Large	3.2 sq. mm.	5 (4 rt.) Upper rt. over-rid. a.s.d.	Patent duct. (No middle lobe of right lung)	RV and PA large, LV and aorta small	Atelectases, espec. of left lung	Congestion of liver and spleen

32	Med. slit: 6 mm.	10 × 20 mm.		1 common stem	Patent duct. Bicuspid rt. A-V valve	Heart very large, RV and PA large, LV small	Compressed by heart. Congestion. Hist. vasc. changes	
34	*intact!*	2 × 4.5 mm.	+			RV and LA large		
36	small med. slit					Heart enlarged, RV large, LA and LV small		
38	Two: 2 × 5 mm. 3 × 5 mm.					RV large, LA small	Congestion	Congestion of liver, spleen, kidney, etc.
39	Size of thin probe		+	3 (1 rt.)	Patent duct.	Heart very large, RV and PA large, LV small	Congestion, edema. Small hemorrhagic infarctions. Small hydrothorax	Congestion of liver, spleen, etc. Small ascites
41	Large med. slit				Art. hypertens. Calcifications of mitral ring	Heart enlarged, RV normal! LV large		
42	Size of a pin		Small		Mitral valve hypoplastic	Heart very large, RV and LA large, LV very small	Congestion, bronchopneumonia	Congestion of liver, spleen, etc.
43	*No* direct communication from pulm. veins to left atrium		Widely patent for. ov.	5 (3 rt.) all opening into sup. vena cava		RA and RV large, LA and LV small	Congestion with alveolar hemorrhages; no hist. vascular changes	Left transv. sinus and int. jugul. vein narrow
44	3 mm.					RA and RV large	Congestion; Histol. changes of arterioles	
45	2 mm.					Heart very large. RV, PA, and LA large, LV very small	Congestion. Atelectasis of left lower lobe.	Congestion of the other organs

TABLE III. NINETEEN CASES OF COR TRIATRIATUM (FROM THE LITERATURE)—(CONT'D)

CASE CASE NO.*	SEX, AGE	CLINICAL SYMPTOMS AND SIGNS	STETHOSCOPIC FINDINGS	ROENTGENOLOGY OF HEART
2	F. 38	Previous hemoptyses (during four pregnancies). Terminally rapidly developing congestive failure with marked dyspnea, rapid, irregular pulse, and precordial pains		
4	F. 11			
5	M. 3			
17	M. ?	Died from suffocation		
18	F. 38	Dyspneic since childhood	PsM apical	
20	F. 1/12	Increasing dyspnea and cyanosis	SM, blowing	
22	? newborn			
26	F. 11	Recurring bronchitis and pneumonia. Delayed development. Cardiac symptoms for only one month: increasing dyspnea. Terminally congestive failure: edema, ascites, liver enlargement	SM	
30	F. 3/12	Dyspnea and extreme cyanosis since birth; venous engorgement and enlarged liver	SM, loud, max. at apex. "Tick-tock-like sound"	Enlarged, globular
32	M. 3/12	Paroxysmal dyspnea and coughing with cyanosis; terminally permanent cyanosis	SM, loud, max. at apex	Considerably enlarged
34	? 4/12	Nil.	No murmur	
36	M. 2	For three weeks nocturnal paroxysms of dyspnea; terminally congestive failure; edema and liver enlargement; lips cyanotic; rapid, irregular pulse; sudden death in extreme cyanosis	SM	
38	M. 18	Cardiac symptoms for only nine months; exertional dyspnea and palpitations; repeated hemoptysis; liver enlargement	DM, rough, during last half of d., max. at left sternal border	Not enlarged

39	F. 1/12	Dyspnea and slight cyanosis; from four weeks of age paroxysms of cyanosis with syncope; liver enlarged, no edema; sudden death in asystolia and heavy cyanosis	SM, loud	Enlarged, globular
41	F. 70	Hypertensive heart disease; grade 4 decompensation		
42	M 2/12	From five weeks of age paroxysms of dyspnea and cyanosis; finger clubbing; moderate anemia; terminally congestive failure; edema, venous engorgement, enlarged liver	No murmur	Generalized enlargement
43	M 2/12	Dyspneic and cyanotic since birth; edema of neck and lower jaw, extending to the face and scalp; flabby; head tilted to the left		Heart diffusely enlarged; bilateral pulm. emphys.
44	F. 6/12	Acutely ill with episodes of severe dyspnea and crying; no cyanosis; tachycardia and liver enlargement; died suddenly	No murmur	Generalized enlargement developed within the last 1½ month
45	M. 1	Delayed development; cardiac symptoms for three months; dyspnea; tachycardia; terminally congestive failure; liver enlargement, edema.	No murmur	Generalized enlargement; left atrium probably relatively enlarged

*Refer to the numbers used in the bibliography (in 1, 6, and 12 details are missing)
SM = systolic murmur
DM = diastolic murmur
PsM = presystolic murmur

The condition is clearly congenital, but the embryology is still open to question and will not be considered here. A critical analysis of the classic theories is given in the paper of Parsons (1950), and other explanations have been suggested by Loeffler (1949) who preferred the term pulmonary sinus, and by Edwards and co-workers (1951) who considered the essential lesion to be a stenosis of the common pulmonary vein.

The anatomy of most of these cases has been rather uniform. A diaphragm subdivided the left atrium into two distinct compartments: a usually greater upper or posterior, often funnel- or wedge-shaped, receiving all the pulmonary veins, and a lower or anterior with the mitral orifice. The auricular appendage always opened into the latter chamber. In one case (No. 30 in the bibliography) the extra chamber receiving the pulmonary veins was situated anteriorly, communicating with both atria. The thickness of the anomalous septum varied from a fraction of a millimeter to a few millimeters, and, histologically, it consisted of fibrous tissue, and generally of heart muscle fibers as well. Usually, one or more perforations existed in the diaphragm, in its center, or peripherally between a free margin and the atrial wall. The border of this perforation was often thickened, probably containing small calcareous deposits. In all cases but one (No. 42) the mitral valve was quite normal.

In two patients (Nos. 22 and 34) the diaphragm was complete and the only pathway of the arterial blood was through defects in the atrial septum, and, in the former case, displaced pulmonary veins. Still another case (No. 43) falls outside the above description, as here no diaphragm existed in the atrium, but all the pulmonary veins opened into a common sinus-like sac behind the heart, draining wholly into the superior vena cava; the only direct connection of this common sac with the left atrium was represented by an atretic cordlike strand.

Associated congenital defects were not very frequent. Most commonly found were atrial septal defects, leading to the upper or lower chamber or both, and an abnormal number of pulmonary veins. Abnormal drainage of the pulmonary veins was only seen in these two cases (Nos. 22 and 43). Two patients suffered from the tetralogy of Fallot, one of them associated with a dextrocardia (Nos. 4 and 5). Finally, a patent ductus was found in three cases, but a continuous murmur was not heard.

Only in one patient (No. 17), dying suddenly from suffocation, did the autopsy definitely fail to demonstrate any circulatory effects of the malformation. Otherwise a cardiac enlargement, mainly because of a right ventricular hypertrophy, was nearly always found, together with signs of a pulmonary congestion, and in most cases congestion of the systemic circulation. It was to be expected that the hemodynamic relations of the uncomplicated cor triatriatum were similar to those of a mitral stenosis, and this was confirmed on heart catheterization in the case reported here. In the presence of an atrial septal defect before the diaphragm the predominant feature may become a left-to-right shunt as in the Lutembacher complex. A septal defect behind the diaphragm was usually associated with cyanosis. In the three cases with a complete obstruction across the left atrium all the blood was mixed in the right atrium, i.e., functionally a cor triloculare; these patients died soon after birth.

Most of the patients died during the first years of life, usually within a few months after birth, and in these patients the perforation in the septum was always small (5 to 6 mm. in diameter or less). Only a few patients with a fairly large opening through the septum reached the adult age. Rather often, symptoms had been slight or absent, until the patient succumbed to a rapidly developing congestive failure. The predominant symptom was dyspnea, in some cases occurring in paroxysms, usually with cyanosis and syncope. It is rather remarkable that real attacks of acute pulmonary edema have never been recorded. Recurrent infections of the respiratory tract and repeated small hemoptyses were also encountered. A clinical history of peripheral embolisms was never obtained, and only in one case (No. 39) the post-mortem examination revealed some tiny infarctions of the lungs.

The stethoscopic findings have been no more conclusive. Frequently, a systolic murmur of varying intensity was heard, especially when an atrial septal defect was present, but also in two cases without any complicating lesions. In two other patients with closed atrial septum a diastolic and presystolic apical murmur was reported. Several patients showed no murmur at all. A rapid, irregular pulse was found in two patients, but it was not proved to be due to an auricular fibrillation.

In eight patients, roentgenograms of the heart were published. Generally the heart shadow was diffusely enlarged, in some cases being almost globular in shape. Pulmonary hilar congestion was also reported. A relative enlargement of the left atrium was suggested only once, and on post-mortem examination a prominent left atrium was not a frequent or characteristic finding in these patients.

Electrocardiograms have only been recorded in three patients (Nos. 38, 43, and 45). As in the present case a right-axis deviation was found with signs of right ventricular hypertrophy. The P waves were never definitely abnormal.

COMMENT

Cor triatriatum is an extremely rare and usually severe disorder of the heart. Most of the patients succumbed during early childhood, and the rest, when not dying from irrelevant causes, sooner or later developed congestive failure which rapidly proved fatal.

The clinical picture was never characteristic. The symptoms have merely been those of a pulmonary hypertension and congestion with a subsequent right ventricular failure, and neither stethoscopy, electrocardiography, nor roentgenography have improved the diagnostic possibilities. Most probably, heart catheterization will always be strongly suggestive of a mitral disease; an apical diastolic murmur and a left auricular enlargement may or may not be present. Angiocardiography has never been applied to these patients. Regarding the possibility of a successful surgical interference, however, this disorder, even if very rare, should be taken into the considerations in obscure cases of pulmonary hypertension, especially when a high "pulmonary capillary pressure" has been measured.

The only way for in-vivo diagnosis at present seems to be an explorative thoracotomy. Before opening the heart, pressure measurements demonstrating a hypertension in the pulmonary veins, but a normal pressure in the left auricle, would be indicative, and after cardiotomy a direct digital exploration of the anomalous structure would afford the necessary details. It should be kept in mind that with the usually employed way of entrance through the auricular appendage the exploring finger will enter in front of the diaphragm and directly upon the normal mitral valve, as actually happened in the case reported here. As the diaphragm was often funnel-shaped in the direction of the blood stream, the way of entrance through a pulmonary vein should possibly be preferred in such case. The splitting of the anomalous structure by finger fracture or by means of cutting instruments should be made as complete as possible, as there is here no valvular function to preserve.

SUMMARY

A case report of a 29-year-old woman with increasing cardiac distress is reported. No murmur could be heard. The heart was not enlarged, but a prominent second left arch and pulmonary congestion were found on the roentgenogram. Moreover, the lower lobe of the left lung was markedly emphysematous. An electrocardiogram showed right ventricular hypertrophy. On heart catheterization, an excessive pulmonary hypertension was found, and the pulmonary "capillary pressure", too, was very high. A mitral disease, therefore, was suggested, and the patient submitted to surgery. Thoracotomy revealed a normal mitral valve, and a normal pressure in the left atrium was measured directly. At post mortem the findings were fully explained, as a transverse septum with only one small perforation was separating the opening of the pulmonary veins from the rest of the atrium (so-called cor triatriatum).

A review is made of the literature concerning anomalous, congenital structures within the left atrium. Thin cords or even broad bands across the lumen have been of no significance. The real cor triatriatum, however, was a serious disorder. Many of the patients died shortly after birth, and only a few reached the adult age. The clinical symptoms and signs were by no means characteristic, and no help was obtained from the usually employed investigations. An in-vivo diagnosis, therefore, must certainly be left for an explorative thoracotomy. The possibility of an effective surgical treatment is briefly discussed.

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A NEW METHOD OF EXTRACORPOREAL CIRCULATION

Deep Hypothermia Combined With Artificial Circulation

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"La condition de la liberté est la fixité du milieu intérieur" (Cl. Bernard)

WHEN Claude Bernard, "Physiology itself" as he has been named, made this famous statement he certainly had not in view the liberty of man undergoing artificial circulation for an intracardiac operation, nor had Cannon this view when he created along the Bernardian line the concept of "homeostasis". The leading idea expressed through the technicalities in this paper are directly related to these views.

If liberty is abandoned, tactically and temporarily, it might then be possible to alter drastically the "milieu intérieur". Although this may look rather sophistic, it seems in the light of recent research that such is really the case.

Perusal of the literature dealing with replacement of the circulation has convinced us that workers in this field have considered it necessary to maintain the normal constants of the body during perfusion. This can only be done by having machines that can deliver the very large amount of fully oxygenated blood necessary for this purpose as well as safe enough to maintain the constants in the oxygen vehicle.

To the present time no such machine or method has been found; at the best their use is limited in duration and any minimal dysfunction is paid in terms of death or irreversible damage. This is a very high price for a none too necessary "liberty."

We have worked with the idea, expressed first in this field by Bigelow, to reduce body temperature. The work of this author has not only been for us informative, but we are glad to say revealing. It will appear that we have not paid great attention to the problem of the machine itself. We considered that it may be possible to make the body adjust to possible and obtainable conditions

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rather than asking a lifeless mechanism to make the proper adjustments. However, we intend in the future to adapt various existing contraptions to the specificities we have to deal with.

We would like to begin this paper by acknowledging how revealing Bigelow's work has been for us and make it known that his example has been the initiation of our personal contribution in this field.

We shall not endeavor in this paper to deal with the numerous problems and possibilities offered by hypothermia as a therapeutic agent. We have already treated this question elsewhere.

During the early period of our work we became convinced that if it were possible to overcome the threatening "cold ventricular fibrillation" hypothermia could be safely used as a therapeutic agent, as well as a help in many surgical problems. We are convinced that deep hypothermia may receive many applications in the future (controlled cicatrization, toxic syndromes of infectious diseases, handling of premature and asphyxic babies, etc.). Already in the United States this method has been used in attempts to treat cancer and psychotic diseases. This, however, was not done under the general principle of decreasing the whole metabolism, and especially in the cases of schizophrenic patients treated by this means, the significance of the results may be questioned. This being considered, it appeared to us that the problem of fully transforming a human being into a real hibernator would not receive proper solution until the physiologic behavior problems linked with both the heart and central nervous system at low temperature are solved.

This strategic aim is worked out in many places from a strictly physiologic view point. The work performed by Penrod and Hagnauer has been particularly revealing to us. We hope that our method might contribute to this particular problem. We then convinced ourselves that the gross biochemical changes taking place during refrigeration were reversible and comparable in many respects to what is seen in the hibernating animal. This has been published elsewhere, and we concluded that these changes could well be considered from a teleologic angle. Since this study showed no real damaging action due to hypothermia, we started the work on extracorporeal circulation combined with hypothermia.

In the course of this study it was hoped that:

(a) We would be able to develop a safe method of cooling and rewarming.

(b) We would gain physiologic information on the significance of the cooling and rewarming changes and particularly ventricular fibrillation.

(c) We could develop a method that would prove safe during intracardiac surgery, since as yet no safe method has been found for this purpose.

Although still lacking the necessary perfection, we believe that the presented method may become such a safe means, and since we are convinced that it is only through the work of many that perfection will be approached, we deemed it advisable to publish this preliminary report.

We apologize for not giving here full credit to the numerous and valuable works we have consulted. However, we have already published a full bibliography on the subject in a previous paper dealing with the generalities of cold, where our sources are fully quoted.

General Description and Leading Ideas of the Method.—Since cold is known to reduce metabolism to a low level this reduction can be used to permit artificial circulation under better conditions. For example 8 or 10 minutes interruption in the function of a perfusion apparatus means death at normal temperature, while it is of minor, if any importance, at 18 to 16° C., rectally.

On the other hand the minute-blood-flow can be reduced to less than a tenth of what is its necessary value at normal temperature.

Finally, since it is not necessary to rewarm fully the experimental animal or the human being submitted to this type of procedure, the postoperative care should probably include maintenance at a reduced body temperature (27° to 28° C.) in order to take advantage of the reduced metabolism during the recovery period. Shock might thus be prevented, in combination with the classical means. We here would take full advantage of this possibility.

During the initial phase of our investigation we tried to develop first a method of perfusion suitable for the considered needs. Here follows the general approach we have used. Dogs are refrigerated to a body temperature where the heart no longer maintains its normal beating. This requires a body temperature of 18° to 15° C. in general. (Ventricular fibrillation usually appears with death as a consequence, if it is of more than 15 to 20 minutes duration in the cold state.) When fibrillation appears the animal is connected to a heart-lung system of reduced size which permits delivery of a maximum of 400 c.c. of blood per minute. A third of this amount is generally sufficient for a 25 kg. dog at 15° C. Since fully oxygenated blood is sent toward the coronaries and the brain, life is maintained during the fibrillation period. This period can be extended at will for hours. (We believe that with a better perfusion method it could last almost indefinitely. Our longest fibrillation time with survival has been 3 hours and 5 minutes with this method. One dog fibrillated for more than 5 hours and was defibrillated and revived.)

Lowering of the body temperature is continued at will or arrested. We have gone as low as 9° C. with revival but ultimate death, after 24 hours. When it is deemed suitable, rewarming is started. Around a temperature of 20° C. the heart is defibrillated through the unopened chest, at times defibrillation appears spontaneously. The animal is then fully rewarmed. Respiration and reflexes reappear; in case of success the animal is normal 30 to 40 hours after the experiment.

At times we have verified during intracardiac operations the value of the method as far as surgery proper is concerned. The main advantages are: (a) almost no bleeding at operation, (b) extremely reduced coronary blood flow allowing a very satisfactory exposure of intracardiac structures.

METHOD

Anesthesia.—Forty-four mongrel dogs weighing from 9 to 35 kg. have been used in this series. After convenient preparation including the use of antihistaminics, and 0.1 ml. per kilogram of body weight of intraperitoneal Nembutal, the animals are anesthetized by means of a drip of a short acting barbiturate (Thiopentone). Ether has also been used with better results as far as the action of the heart is concerned.

Preliminary Surgery.—The femoral artery is connected to a mercury manometer. Through the femoral vein, a large bore plastic cannula is placed into the higher part of the inferior vena cava. Through the jugular vein, another catheter is lowered to a level just overlying the entrance of the superior cava in the right auricle. Through the carotid artery in the same side, a cannula is placed downward and one upward.

Clotting.—Clotting time is prolonged during cold, and presumably also is the length of time during which heparin is active allowing for reduced dosages of the drug.

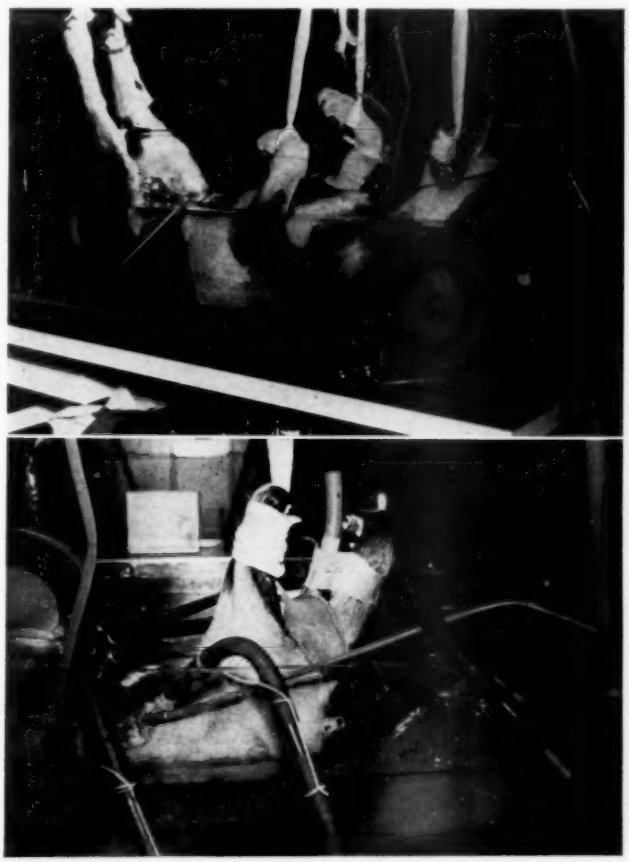
Other Controls.—The three standard leads of the electrocardiogram are serially recorded. The temperature is read from a long mercury thermometer frequently checked and placed 15 cm. in the rectum. In a few instances arterial and venous O_2 determinations have been made. We have recently started a study of the circulation dynamics during refrigeration and perfusion by means of angiocardiography. This will be presented in another paper. Shivering is controlled by means of added Thiopentone or curare. It ordinarily stops at a temperature of 25° to 24° C. (under barbituric anesthesia). Special attention is paid during perfusion to the minute blood flow delivered by the machine. In this paper we do not intend to enter fully into the details of this method but simply express our results on a gross basis.

Refrigeration.—Once the preliminary surgery has been performed dogs are immersed in an iced bath, with their paws hanging from an attachment located above the bath (Fig. 1, A and B). Attention is then paid to the temperature and other variables. The treatment in all dogs except an uncooled control series of seven dogs has been similar to the point when perfusion starts.

Perfusion is started either when the heart shows electrically and on the manometer signs, which we believe to be signs of stress, or after ventricular fibrillation has set in.

It seems convenient to distinguish here the two different methods of oxygenation we have been using in two series. When the necessity to start perfusion appears, respiration has stopped ordinarily around a rectal temperature of 20° C., and shivering has been fully controlled. The animal is connected to the machine and perfusion starts.

A.



B.

Fig. 1.—*A*, Method of cooling. *B*, Catheters in place ready for perfusion.

Group A.—In this group the machine for brain perfusion designed by Professor Crafoord and described by V. O. Björk was used for the perfusion of the entire dog. The regulator and the pumps are of the model used and designed by Å. Senning.

The enormous reduction in metabolism rendered possible by reduced body temperatures made us deem it advisable to use a small machine. No blood was used to fill this oxygenator, but only saline. Three series of dogs should be distinguished in this group: series A 1, A 2, and A 3.

In series A 1: (Cases 64, 84, 85, 89)* This was done at normal body temperature as a control series. Perfusions lasting from 50 min. to 240 min. were performed. After the perfusion the dogs were placed back into their cages with no further help.

*The case numbers are given for easy reference to tables. On the other hand, a few selected case reports are given in appendix as examples.

TABLE I. EXTRACORPOREAL CIRCULATION IN THE HYPOTHERMIC DOG WITH VENTRICULAR FIBRILLATION AND DEFIBRILLATION THROUGH THE UNOPENED CHEST*

EXPERIMENT AND NUMBER	DOG NO.	FIBRILLATION		DEFIBRILLATION						FAILURES AT DEFIB.		DIED		RECOVER	
		NUMBER OF		SPONTANEOUSLY		WITH SHOCKS		TOTAL DEFIB.							
		N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
7 Perfusion with disk oxygenator at normal temperatures	7	0	0	0	0	0	0	0	0	0	0	4	57	3	43
15 Perfusion with disk oxygenator at low temperatures	14	15	100	0	0	13	87	13		1	6.6	14		1	
14 Perfusion with donor lungs at low temperatures	13	17		4	0	11		15		2		8		6	
8 Intracardiac surgery with extracorporeal circulation at low temperatures	6	19		5	26	12		17	8.5	0	0	8	100	0	0

Total per cent:
Number of dogs perfused: 44
Number of dogs fibrillating: 33
Number of fibrillations: 51
Number of defibrillations: 45
Number of failure at defibrillations: 3
Number of deaths: 34
Number of recoveries: 10

Note: The per cent of defibrillation is given in relation to the number of fibrillations not of dogs. Accordingly, the per cent of failure is related to the number of fibrillations. The per cent of dead or recovered relates to the total number of dogs in each series. This table is broken down in Table IA. The discrepancies in percentages noted in this table are explained by the fact that certain experiments were arrested by death due to another cause than ventricular fibrillations, such as acute pulmonary edema, etc.

*Controls perfused at normal temperature and not fibrillating and intracardiac surgery done during perfusion at low temperature.

In series A 2: (Cases 72, 76, 77, 80, 83) Perfusions were started either before or after ventricular fibrillation during hypothermia. Dogs were defibrillated through the unopened chest at a favorable time during rewarming and perfusion used therefrom as a help during rewarming.

In series A 3: Intracardiac surgery was performed during perfusion at a low body temperature.

Group B.—Here again two series must be considered.

Series B 1: In this group the oxygenator was replaced by a pair of freshly donated lungs (Fig. 2) from another animal placed in proper connection with the cannulas set previously into the experimental animal, and rhythmically inflated with O_2 or air. The same method of defibrillation was used when necessary. Spontaneous defibrillation often makes it unnecessary to defibrillate by means of shocks.

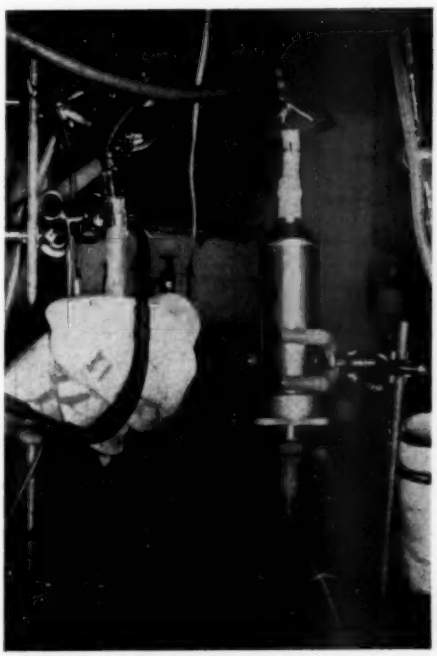


Fig. 2.—Setup when using fresh donated lungs to oxygenate blood in the artificial heart. Note pumps, filter, and the donated lungs.

Series B 2: The method was the same differing only by the fact that intracardiac surgery was performed during perfusion.

Defibrillation Method.—At times defibrillation occurred spontaneously either during further cooling or during rewarming and perfusion. In many cases it was necessary to defibrillate the animal. Since we were interested in a proper evaluation of the results, it was necessary to use a method that would permit such a process without opening the chest. The method, offered by Statteford and Guitton at normal temperature, was the answer with some modifications, but the necessary power was much lower than theirs and especially the amount of current necessary which was never above 10 amperes at 50 cycles. At times potentials of 400 volts have been used. Mostly potentials of 180 to 250 volts were sufficient. The electrodes were 12 to 16 cm. in diameter and were applied by means of a rubber band on each side of the chest overlying the heart. They are then ready for use instantaneously. The advisability of having at hand such a method in human cardiac catheterization needs no further emphasis.

THE BEHAVIOR OF THE BLOOD PRESSURE AND PULSE RATE DURING THESE EXPERIMENTS

For clarity we will emphasize mainly the observations made with the donated lungs used as oxygenators. At times similar pictures were seen with the disk oxygenator, but since we used this apparatus in the beginning of our experience it seems unsuitable to draw too many conclusions from what may have been an inadequate use. On the other hand, case reports are available in this paper giving the necessary information about the observations recorded when using Crafoord-Björk's oxygenator.

As is known, blood pressure decreases during cooling. When fibrillation appears it drops to zero, unless perfusion has been started prior to this accident. In any case under "cold perfusion" the blood pressure varies between 30 and 40 mm. Hg during fibrillation. At times we have seen it at very low levels of 10 or 15 mm. Hg. We now believe that this should be avoided. When rewarming starts the blood pressure does not show any variations at first. When the body temperature is increasing, the blood pressure under ideal conditions rises parallel. When defibrillation occurs the blood pressure continues its rise toward pre-immersion level. At present, this is consistently the case in all of our dogs.

Until rather recently, we have been concerned with great irregularities and sudden drops in blood pressure during rewarming despite pressor substance administration (see Case Reports).

This indicated (a) an inadequacy of the vasomotor centers being due either to faulty perfusion, and/or (b) a possible cardiac inadequacy.

With this in mind we decided to stop the perfusion of the heart early after defibrillation, continuing only the brain perfusion and that going toward the right side of the heart. It seems to us that to direct a flow of blood toward the carotid artery and the aortic valves can within limits be similiar to an aortic stenosis. It seems therefore unwise to force this extra work upon the heart at a time when all its reserves are needed.

Accordingly, this type of perfusion (toward the coronaries) is now performed in discontinuous and short periods. Once fibrillation has been controlled we keep it continuous. Before fibrillation we also use the same method of discontinued short periods of coronary perfusion. Figs. 3C and 3D illustrate our views on this problem. Since we have started this procedure we have observed a return to preimmersion levels of the blood pressure without the use of any pressor substances in most instances. At times, unstable blood pressure is observed. In such instances our "working hypothesis" is that brain damage is responsible for this particular behavior.

Pulse Rate.—A complete study of this factor is under preparation. We wish only to emphasize that the thermal increment affecting the cardiac pacemaker is responsible for the lowering of the pulse rate only within limits. In any case the influence of factors such as peripheral reflexes, cardiac vascularization and/or central nervous action comes into full action at the very low temperatures. Thus we can with the present method convert, as we have said, standstill into normal beating, or a very slow pulse rate into a faster one (Figs. 3 and 4, E-H).

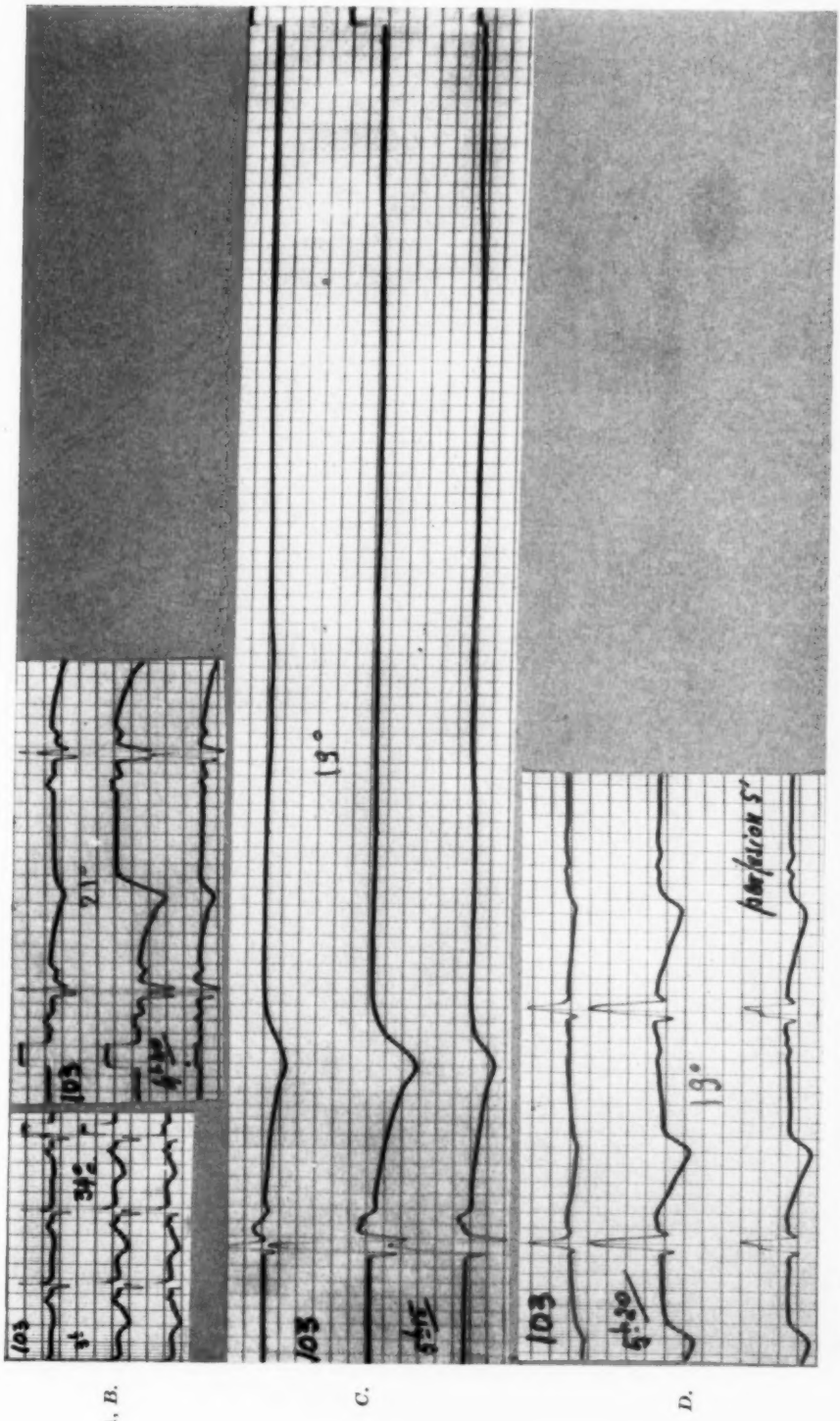


Fig. 3 (Case 103).—See case report. *A* and *B*, Notice progressive lengthening of electrical systole. *C* and *D*, Heart has slowed down to one beat every two minutes. Five-minute perfusion brings back more normal pulse.

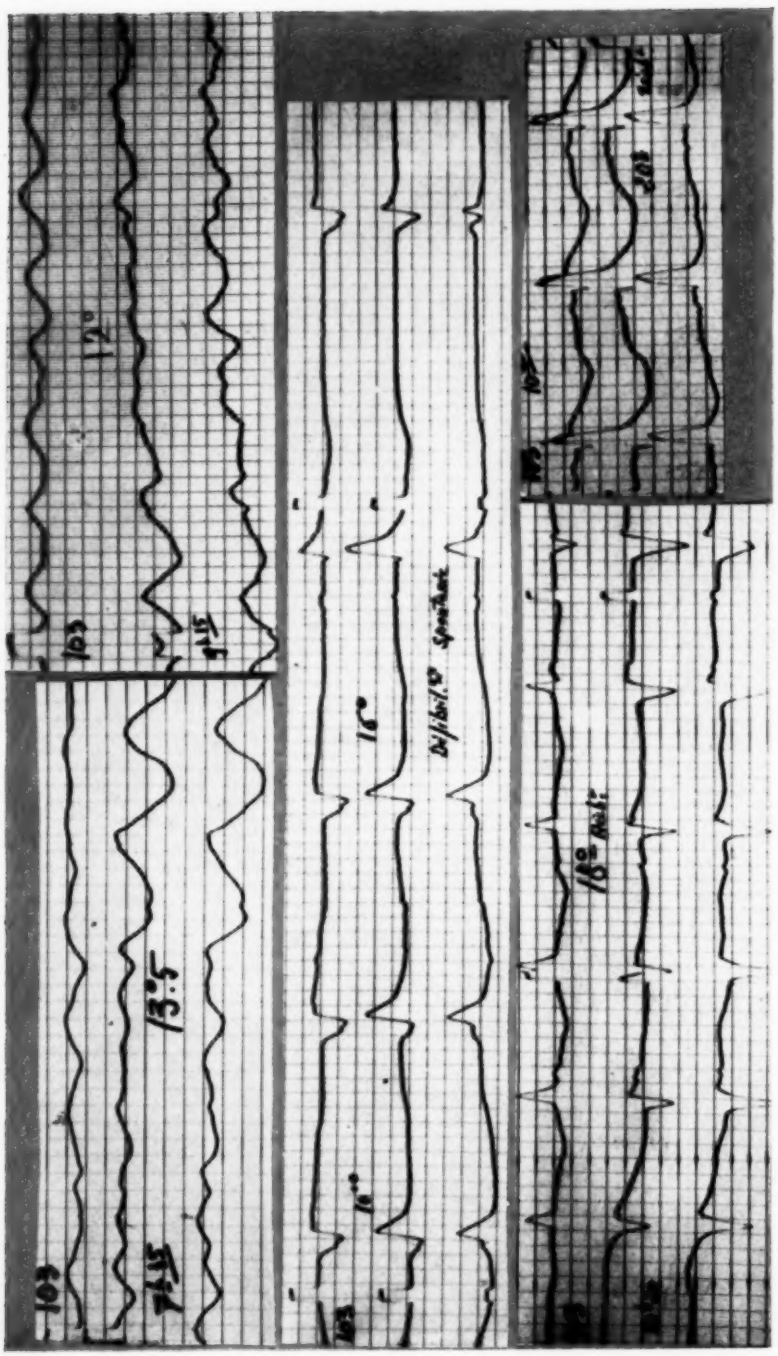


Fig. 3.—*E* and *F*. Aspects of ventricular fibrillation under perfusion at various intervals and temperatures. *G*, During rewarming heart goes back spontaneously to normal beatings. *H* and *I*. Aspects of electrocardiogram during first phases of rewarming.

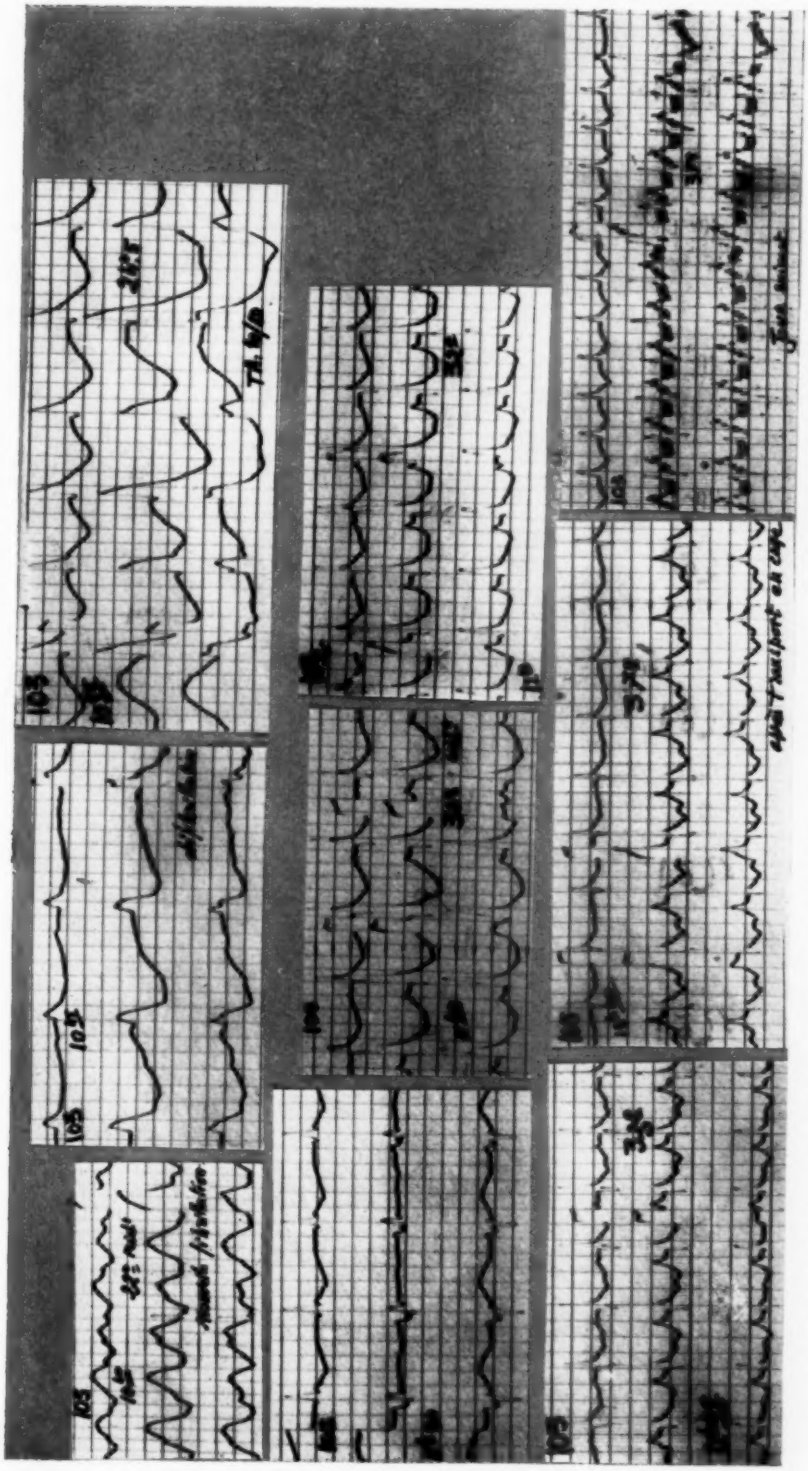


Fig. 3.—*J*, During rewarming heart fibrillates again. Perfusion maintains proper coronary circulation. *K*, Heart is defibrillated with one electroshock. *L*, *M*, *N*, *O*, *P*, *Q* show aspects of electrocardiogram during last phases of rewarming. *R*, Electrocardiogram recorded on following day. Dog survived in good condition.

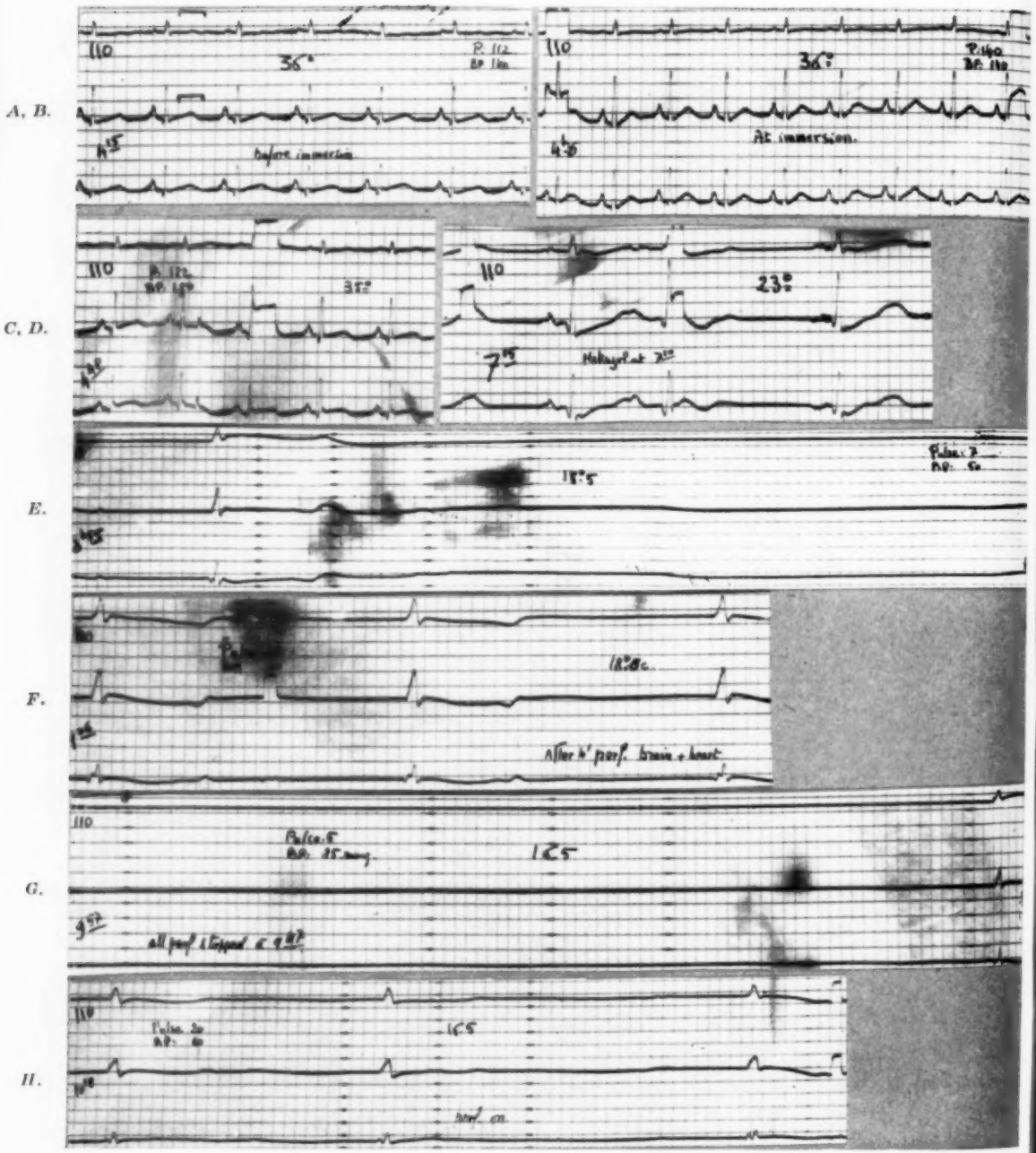


Fig. 4, *A-H.* *(For legend see opposite page.)*

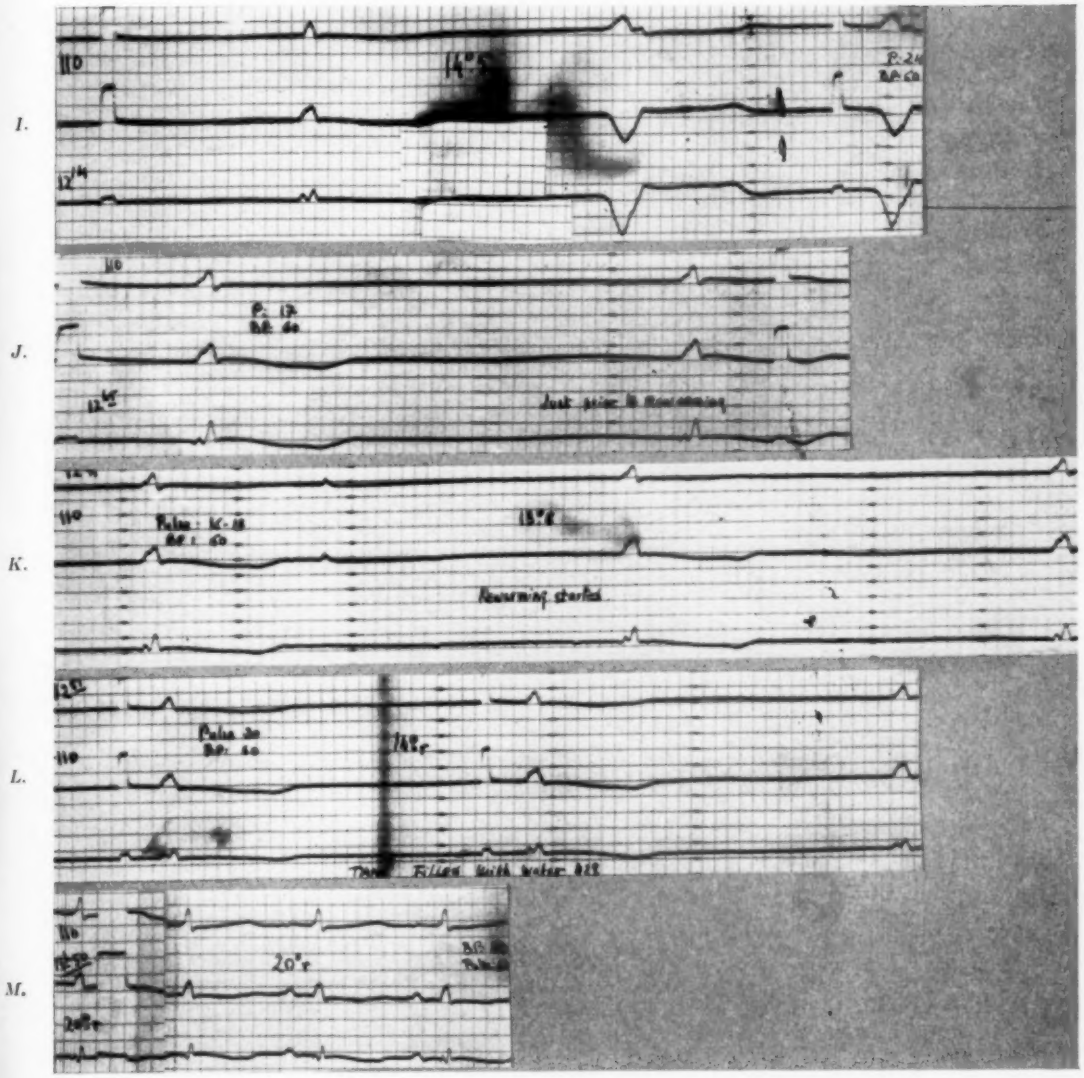


Fig. 4, *I-M.*

Fig. 4 (Case 110).—See case report. A series of electrocardiograms in the three standard leads recorded during an experiment of artificial circulation with lowering of the body temperature. Emphasis is not placed upon the electrocardiographic changes proper but rather upon the effects of cold and/or perfusion on the heart rate. *A*, Electrocardiogram prior to immersion into iced water. *B*, Just at immersion time. Under proper anesthetic protection pulse increases slightly; blood pressure remains stable. *C*, 35° C. Blood pressure has gone up moderately. Electrocardiogram is normal. *D*, 23° C. Gross electrocardiographic changes, especially according to our hypotheses, important lengthening of the *P-T* interval. *E*, 18.5° C. Pulse rate slowing as much as 7 per minute. The deflection which appears starting at T belongs to electrical systole. *F*, 18.5° C. Cooling proceeding, brain and coronary perfusion started. This tracing emphasizes dramatically the influence of proper coronary blood flow and blood pressure head upon the heart rate in cold. This electrocardiogram was recorded 4 minutes after starting perfusion. Pulse has gone from 7 to 23 per minute; since cold is known to reduce pulse rate, this acceleration can only be due to better blood flow. *G*, 16.5° C. Perfusion was stopped 10 minutes before this electrocardiogram was recorded. Throughout this period only an occasional heart beat occurred. *H*, When blood perfusion was started again pulse rate incresed almost instantaneously and came up to 20/min. This emphasizes again the utmost importance of proper coronary blood flow during refrigeration.

I, *J*, *K*, *L*, *M*, Show the influence of low temperatures on heart action. Pulse rate is slowly decrasing as is seen in the hibernating animal. Notice in *L* that immersion in warm water sets immediately a faster rate, thus indicating (perhaps) an ever present reflex ability during deep hypothermia.

These details are of fundamental interest in the general problem of cardiovascular behavior during cooling. They are of equal interest when it comes to the problem of controlling the appearance of fibrillation. We believe that this method will offer, when fully developed, such a possibility of control. We shall in the discussion emphasize the use that can be made of this possibility.

Lowering of Body Temperature.—As may be seen from the tables, the reductions in body temperature have been drastic; in one case it went down as low as 9° C., and the animal was fully restored to 37° C. (see Case report 124). We do not believe that for the use considered it would be necessary to apply such low temperatures to human beings. A temperature of 16° to 14° C. or maybe a little higher may prove satisfactory in combination with extracorporeal circulation.

We wanted, however, to ascertain the feasibility of reviving an animal after its temperature had dropped to extremely low levels. It must also be remembered that the aim expressed first by Bigelow, which would be to operate without any machine, would involve lowering of the body to even lower levels (such as 4° to 5° C.) in order to permit exclusion of the heart during long periods, as is possible in the hibernator. One animal survived indefinitely after being cooled to a temperature of 12° C. It must be mentioned that this animal had a 7-hour perfusion and that its heart fibrillated during 3 hours and 5 minutes (see Case Report 103, Fig. 3).

From the fact that the mean temperature during cooling of the surviving animal is not significantly higher than that of the others we conclude that the level of reduction in body temperature during these experiments is not a factor in terms of survival.

Some idea of the electrocardiographic changes prior to fibrillation at the very low temperatures can be gained from Figs. 3 and 5 to 8 as well as from other case reports in this paper.

ONSET OF FIBRILLATION

(a) In some cases we deliberately waited until fibrillation appeared due to cold and related factors. The perfusion was then started. Details about the possible mechanism of fibrillation in cold will appear elsewhere. Figs. 5, 7, 9 and 10 show fibrillation at the onset as recorded by the electrocardiograph. It has been our observation, although not yet warranted by statistical analysis, that high (relatively) blood pressure results in a delay in fibrillation under certain conditions. In this respect we have found that antihistaminics are useful for maintaining a rather high blood pressure. The following statements are informative in this respect, although the statistics have not been validated: Mean blood pressure at 20° C. in 17 dogs who did not receive antihistaminics prior to cooling was 51.9 mm. Hg. Mean blood pressure at 20° in 20 dogs who received antihistaminics prior to cooling was 100.5 mm. Hg.

(b) In other cases we attempted to start perfusion before fibrillation in order to verify if the improvement resulting in the coronary circulation would delay

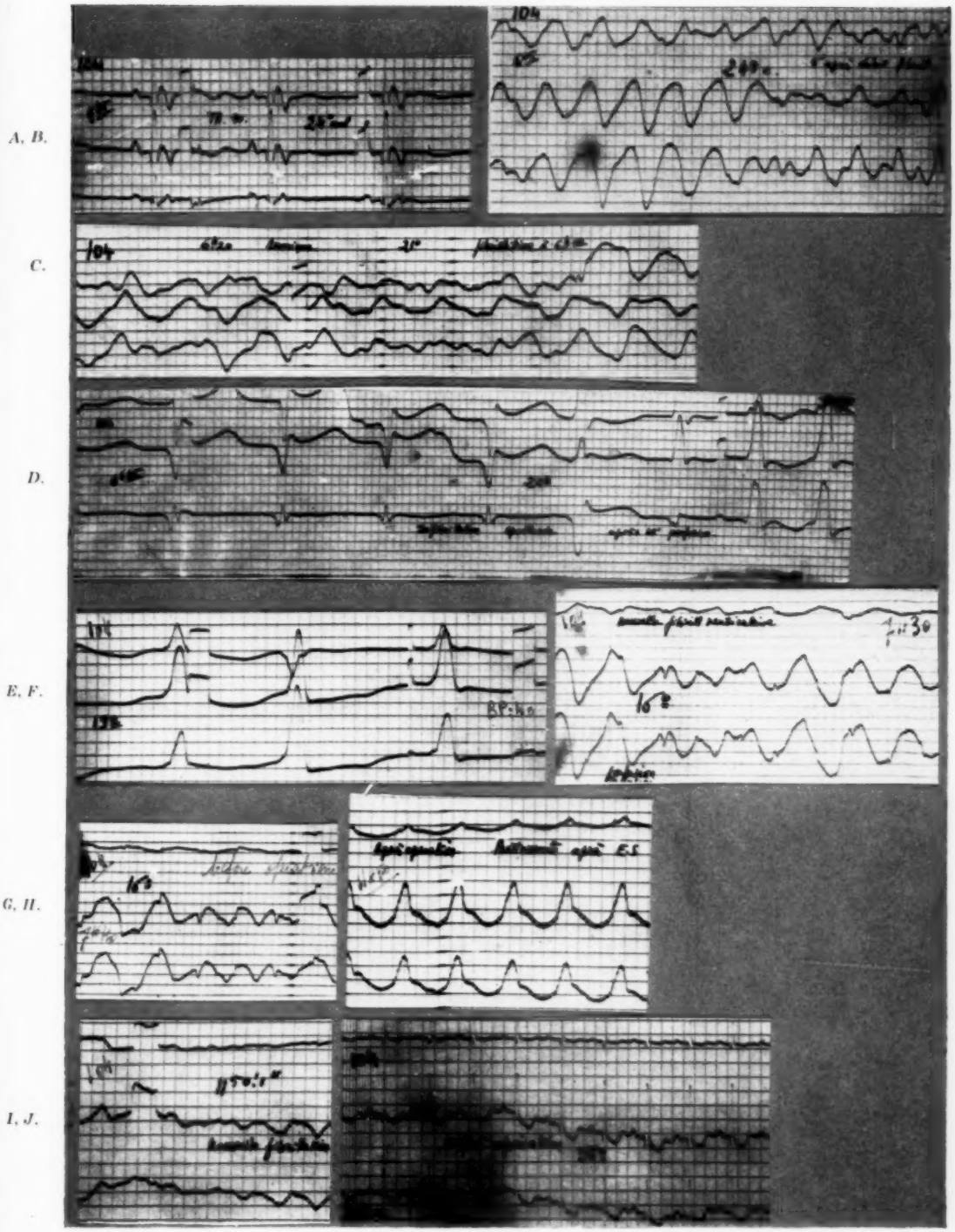


Fig. 5 (Case 104).—*A*, Notice altered electrocardiogram at a relatively high temperature. *B*, Five minutes after fibrillation started. *C*, Fibrillation, notice rhythmic waves. *D*, Spontaneous defibrillation. *E* and *F*, Just before operation. *H* and *I*, Defibrillation and fibrillations after operation. *J*, 35 degrees after operation.

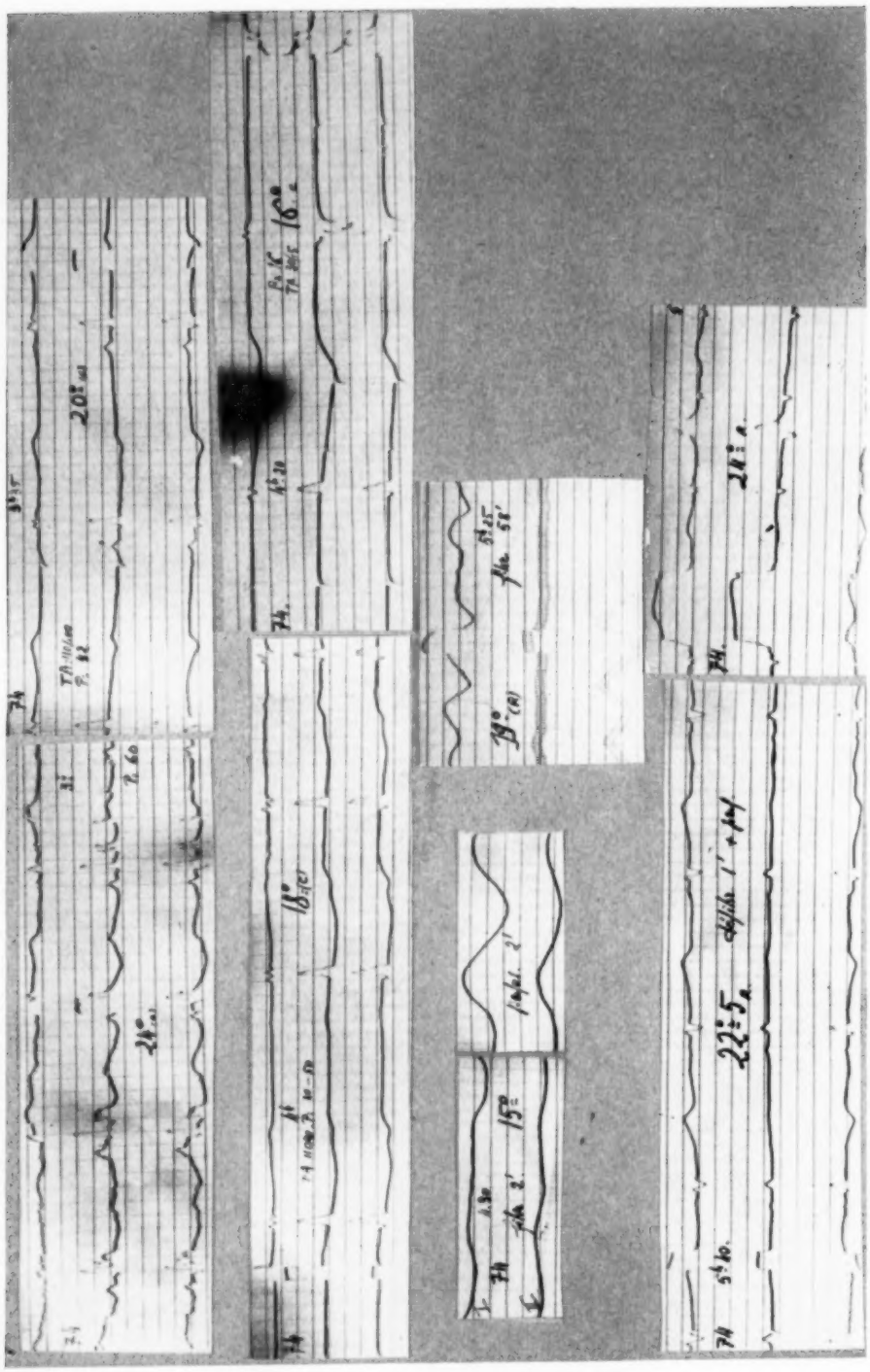


Fig. 6 (Case 74).—See case report. *A* to *D*, Progressive lengthening of P-T interval. *E*, Aspect of electrocardiogram after two minutes ventricular fibrillation. Perfusion on. *F*, Fibrillation going on (58 minutes) under perfusion. Rewarming started, observe increased amplitude of fibrillating waves. *G*, Defibrillation with shocks. *H*, Low voltage in electrocardiogram. This dog died 10 to 12 hours after complete rewarming.

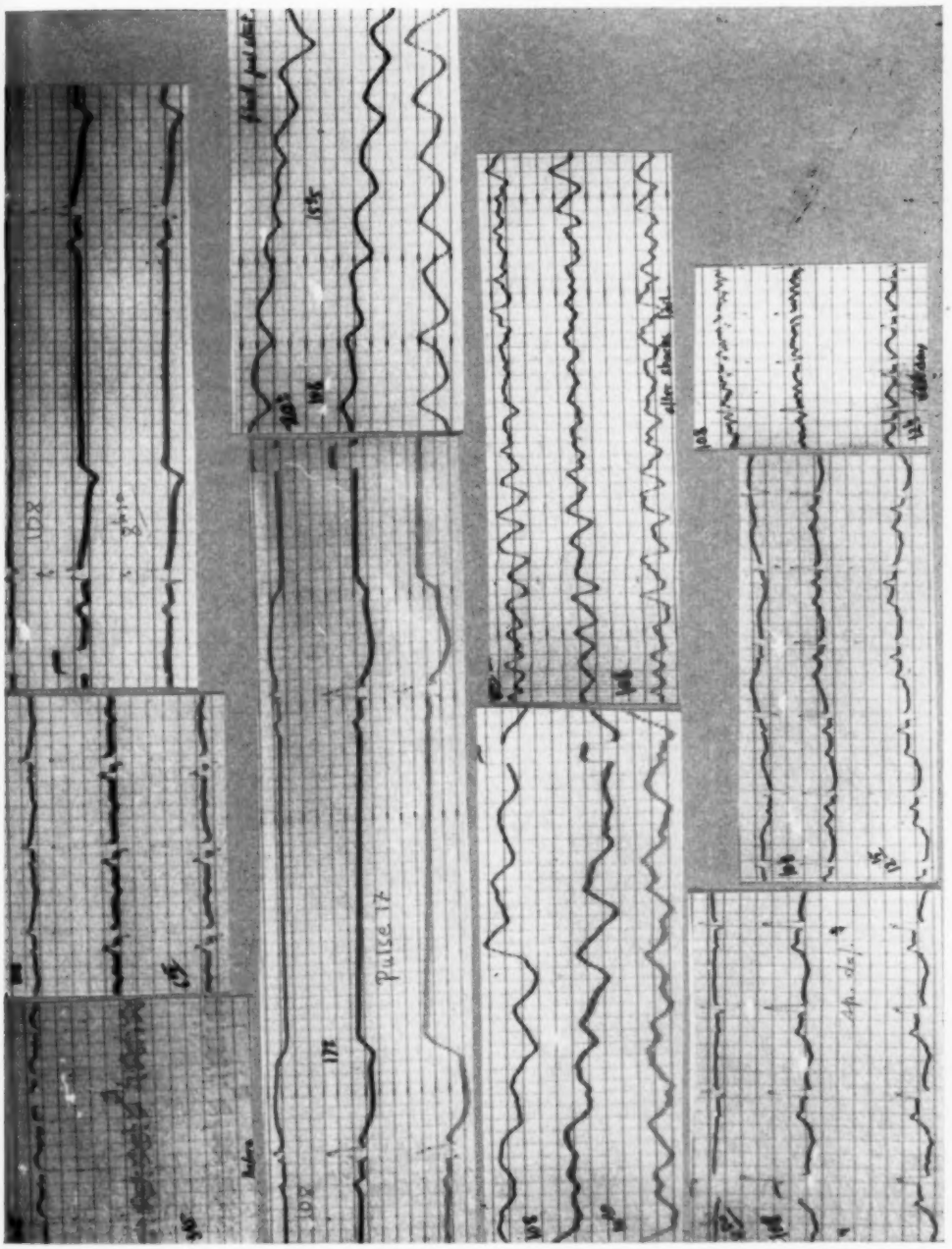


Fig. 7 (Case 108).—*A*, Just before immersion. *B*, At 27° C. *C*, 19° C. *D*, *E*, *F*, Aspects of electrocardiogram just prior to fibrillation and during fibrillation with perfusion. *G*, One shock, 300 volts, 5 amperes, has been delivered without effect. Fibrillation proceeds. *H*, After rewarming has brought temperature 3 degrees higher, spontaneous defibrillation occurred. This emphasizes the innocuity (apparent) of such shocks at low body temperatures. *I*, 28° C. during rewarming. *J*, Electrocardiogram recorded one day after experiment. This animal survived without giving any trouble at any time.

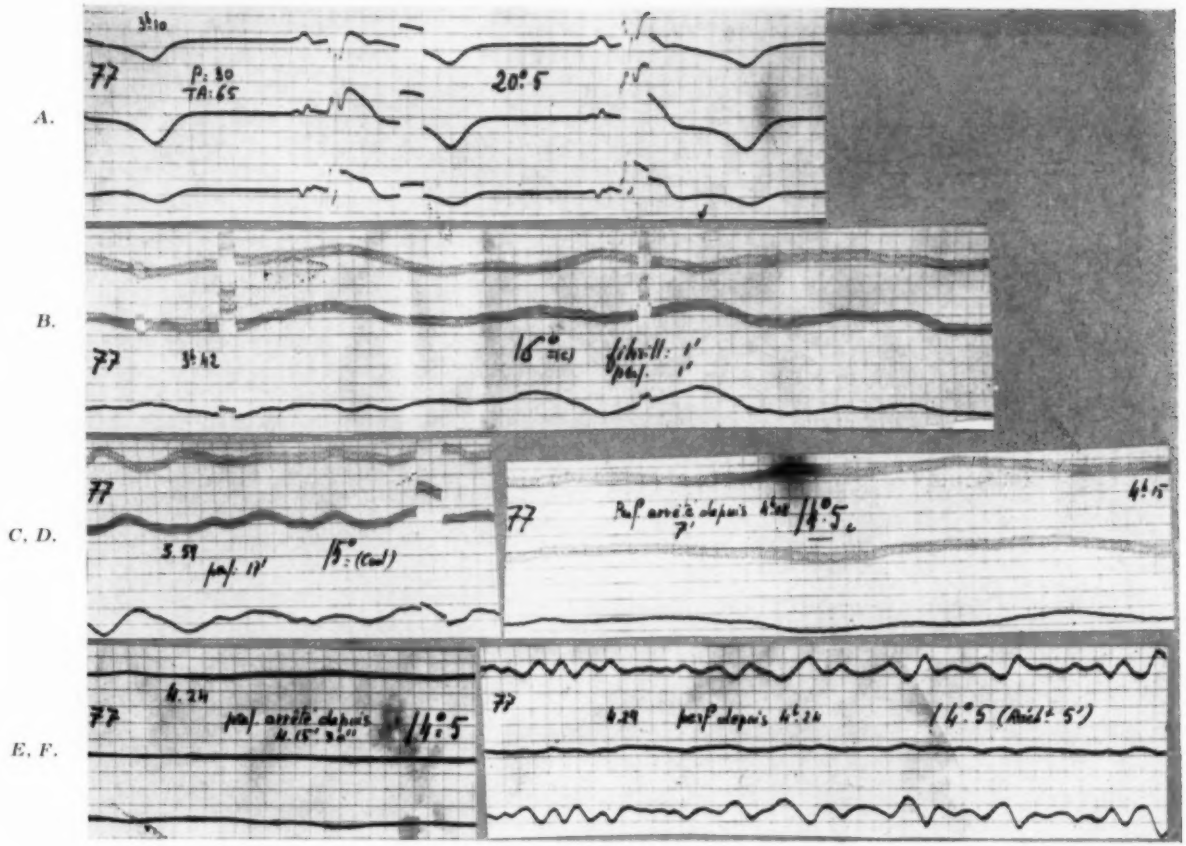


Fig. 8 (Case 77).—The effect of coronary circulation upon the fibrillating waves. *A*, Prior to fibrillation. *B*, Fibrillation one minute prior to record, perfusion started at the same time. *C*, On further cooling, notice the increased rate of waves: this paradoxical aspect may be due to proper coronary circulation. *D*, Perfusion has been stopped purposely 7 minutes prior to record. Notice flattening of curve. *E*, Perfusion was started again and then stopped; the record shows again the influence of inadequate coronary blood flow. *F*, Recorded 5 minutes after perfusion was started again. Notice fast rate which may be in correspondence with rewarming which was started at the same time.

TABLE IA

DOG NO.	TEMPERATURE OF FIBRILLATION WHEN PERFUSION WAS STARTED PRIOR TO FIBRILLATION		DOG NO.	TEMPERATURE OF FIBRILLATION WHEN PERFUSION WAS NOT STARTED PRIOR TO FIBRILLATION
	TEMPERATURE AT WHICH PERFUSION STARTED (°C.)	TEMPERATURE WHEN FIBRILLATED OR WHEN REWARMING STARTED (°C.)		TEMPERATURE WHEN FIBRILLATED (°C.)
67	22	19	74	15
68	22	17	76	17 off bath for oper.
69	20	18	77	16
71	18	13 (13.5r)	79	20
72	20	18	80	20
73	20	15 (15r)	83	16.5
75	20 oper.	20 off bath	86	22.5
81a	19	17	87	20
82	20	18 oper.	94	20
82a	19	16 (16r)	95	21
90	17	15.5	97	23
96	17	16	99	20
98	12	12	102	11.5
100	17	16	104	24
101	16	14 off bath	105	24
103	19	13.5	106	21
107	20	16.5	108	15.5
			109	24

Number of dogs: 17
Number of cooling fibrillations: 13
Number of rewarming fibrillations: 4
Mean temperature of perfusion: 18.7
Mean fibrillating temp. during cooling: 15.8
Mean fibrillating temp. during rewarm.: 14.2

Number of dogs: 18
Number of cooling fibrillations: 18
Number of rewarm. fibrillations: 0
Mean temp. of fibrillation: 19.3

r: Rewarming

the fibrillation time. Table IA shows the difference. This table must however be interpreted cautiously since it is obvious that both groups are not comparable. In the first group it can be noticed that perfusion temperatures are located around 20°C. or lower, while in the other group we have often noted fibrillation at 24° C. These cannot then be compared. In order to settle this problem we should have started the perfusion at a nonlethal temperature.

However, although it is impossible to give a statistical appreciation, we feel strongly that perfusion as we handle it now is effective in delaying the appearance of fibrillation. In agreement with this theory is the fact that many of the fibrillations observed during rewarming occurred after the animal was rewarmed from very low temperature without fibrillation at any time during cooling. The rewarming fibrillations are still mysterious in nature (possibly due to metabolic disturbances in the cardiac nodes, not in the muscle). In any case, defibrillation is always easy to produce in such cases.

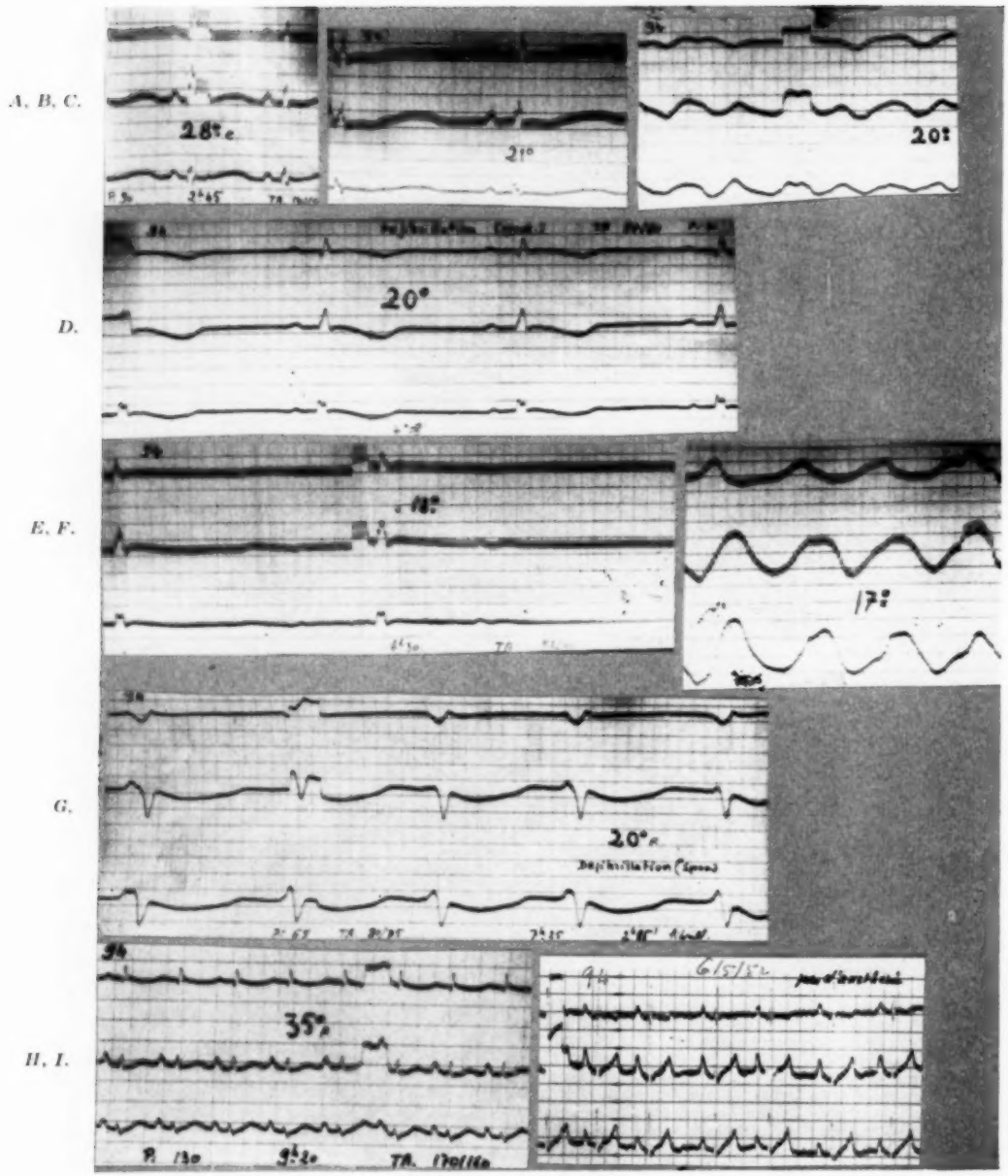


Fig. 9 (Case 94).—Perfusion during deep hypothermia. Spontaneous defibrillation *C* to *D*, during cooling. *F* and *G*, Spontaneous defibrillation during rewarming after correct perfusion. *H*, Aspect of electrocardiogram during last phase of rewarming. *I*, Electrocardiogram recorded three weeks after experiment. (Electroencephalogram was normal as well.)

BEHAVIOR DURING FIBRILLATION AND DEFIBRILLATION

As can be seen in the Tables I to V, our fibrillating times are rather extended. This was permitted in order to be sure that the whole circulation was really replaced by the machine, during this interval. With this approach to the problem there is every reason to believe that when a completely satisfactory method of perfusion is perfected, there will be but little difficulty in applying it as far as surgery is concerned. This is why we have stopped performing operations in this series since nothing could be gained from them as far as information in terms of perfusion technique was concerned.

TABLE II. PERFUSION DURATION IN THE HYPOTHERMIC DOG AND FIBRILLATION DURATION WITH INDICATION OF THE DEFIBRILLATION TEMPERATURES AND OF THE COOLING RECTAL TEMPERATURES

GROUPS AND SERIES	PERFUSION DURATIONS	FIBRILLATION DURATIONS	COOLING TEMPERATURES (°C.)	TEMPERATURES OF DEFIBRILLATION (°C.)
Group A, (Disk oxygenator) Perfused at normal temperature; series A1 (7)	1 hr. 57 min. 0.50-4.00	none	none	none
Surviving in series A1 (3)	1 hr. 45 min. 0.25-4.00	none	none	none
Perfused at low body temperature, series A2 (15)	2 hr. 43 min. 1 hr. 15 min.-4 hr. 45 min.	1 hr. 35 min. 0.50-3.20 (14)	15.9 13-20 (15)	23 20-25 (12)
Surviving perfusion and fibrillation at low body temperature in A2 (1)	1 hr. 25 min. (1)	0.45 (1)	17 (1)	20 (1)
Group B1, (oxygenation by means of a donated pair of lungs) (14)	3 hr. 51 min. 1 hr. 30 min.-7.00 (14)	2 hr. 39 min. 1 hr. 30 min.-4 hr. (13)	14.7 10.5-20 (14)	21.6 17.5-26 (11)
Surviving from series B1 (6)	3 hr. 42 min. 2 hr. 47 min.-7 hr. (6)	2 hr. 36 min. 1 hr. 55 min.-3 hr. 15 min. (5)	15.5 12-16.5 (5)	21.3 20-23 (5)
Group A3 + group B2, operated dogs 7, no survival	3 hr. 10 min. 0.15-6.05 (7)	2 hr. 19 min. 0.15-5 hr. 50 min. (5)	17.5 14.5-20 (8)	22 18.3-25.0 (4)

In group A, series A1, one animal did not fibrillate. In series B2, one animal did not fibrillate. In the operated series done early in the experiments, some dogs died, before the operation was over, from air bubbles. These details explain some discrepancies in this table.

The first number given is the mean of values, the following numbers underlying the first are expressing the range. The number in brackets indicates the number of animals in each item.

During fibrillation, perfusion proceeds continuously from vein to carotid up and downward. Figs. 3, 5, 7, and 11 are illustrative of ventricular fibrillation at various intervals.

We have verified that nutrition by the coronaries is essential in maintaining what we are forced to term "a satisfactory fibrillation." Figs. 7 and 8 give an idea of what is meant by this concept. At times we have started perfusion after

the onset of fibrillation, sometimes several minutes after; in such cases the waves are weak (Fig. 12, A) and of low amplitude. After several minutes of perfusion waves are faster and of greater amplitude (Fig. 12, B).

Fig. 8 shows the influence of perfusion on the fibrillation as shown by the electrocardiogram. In this case perfusion was interrupted deliberately and

TABLE III. DURATION OF PERFUSION IN DOGS AND DURATION (MINUTES) OF FIBRILLATION WITH INDICATION OF THE TEMPERATURES OF DEFIBRILLATION AND OF THE MEANS BY WHICH THE DEFINITIVE DEFIBRILLATION WAS OBTAINED (INCLUDING OPERATED DOGS)

DOG NO.	PERF. DUR. (MIN.)	FIBR. DUR. (MIN.)	TEMP. AT DEFIBR. (°C.)	METHOD OF DEFIBR.	DIED	SURVIVED	COOLING (°C.)	TYPE OF EXPERIMENT
64	50	no	no	no	+	—	not	Perfusion at normal temperature using disk oxygenator
65	50	no	no	no	—	+	not	
88	180	no	no	no	+	—	not	
89	220	no	no	no	+	—	not	
91	60	no	no	no	+	—	not	
92	25	no	no	no	—	+	not	
85	240	no	no	no	—	+	not	
66	75	no	no	no	+	—	20°	Perfusion at low body temperature using the disk oxygenator
68	135	60	25	shocks	+	—	17	
69	230	50	20	shocks	+	—	17.5	
71	215	70	24	shocks	+	—	13	
72	85	45	24	shocks	—	+	17	
74	85	70	22.5	shocks	+	—	13.5	
77	140	140	not	pulm. ed.	+	—	13	
78	130	105	22	shocks	+	—	17	
80	285	200	25.5	shocks	+	—	13	
81a	230	105	23	shocks	+	—	17	
82a	185	25	22	shocks	+	—	16	
83	105	80	22	shocks	+	—	16	
87	145	120	imposs.	shocks	+	—	19	
90	160	130	22	shocks	+	—	15.5	
73	240	130	24	shocks	+	—	15	
93	170	no fib.	no	no	—	+	20°	Perfused at low body temperature, using a pair of donor lungs as oxygenator
94	167	142	20	spont.	—	+	16.5	
95	225	205	24	shocks	+	—	16.5	
96	240	170	21	shocks	—	+	14.5	
97	247	100	21	shocks	+	—	15	
98	90	90	not	done	+	—	12	
99	185	155	21	shocks	—	+	15	
101	210	120	21	shocks	+	—	10.5	
103	420	195	21	shocks	—	+	12	
105	220	190	not	failure	+	—	16	
106	330	240	26	shocks	+	—	14.5	
107	280	180	23	shocks	+	—	15	
108	150	115	23	spont.	—	+	15	
109	300	165	17.5	spont.	+	—	14	
75	50	40	not	pulm. ed.	+	—	18	Operated with heart open during perfusion at low temperature. Lungs, disks
76	not	recor.	dead	—	+	—	17	
82	15	no fib.	no	air emb.	+	—	19	
84	160	no fib.	no	no	+	—	19	
86	205	15	20	shocks	+	—	20	
100	365	350	25	shocks	+	—	16	
101	240	90	18.3	spont.	+	—	14.5	
104	300	200	25	shocks	+	—	17	

started again several times during fibrillation. More details and a complete study of our observations about fibrillation will appear later.

We have also made direct observations of ventricular fibrillation at low temperatures during operations with the thorax and heart open. The perceptible waves are of low amplitude and extremely slow. The usual "bag of worm" aspect and feeling are here replaced by a "bag of snakes" impression.

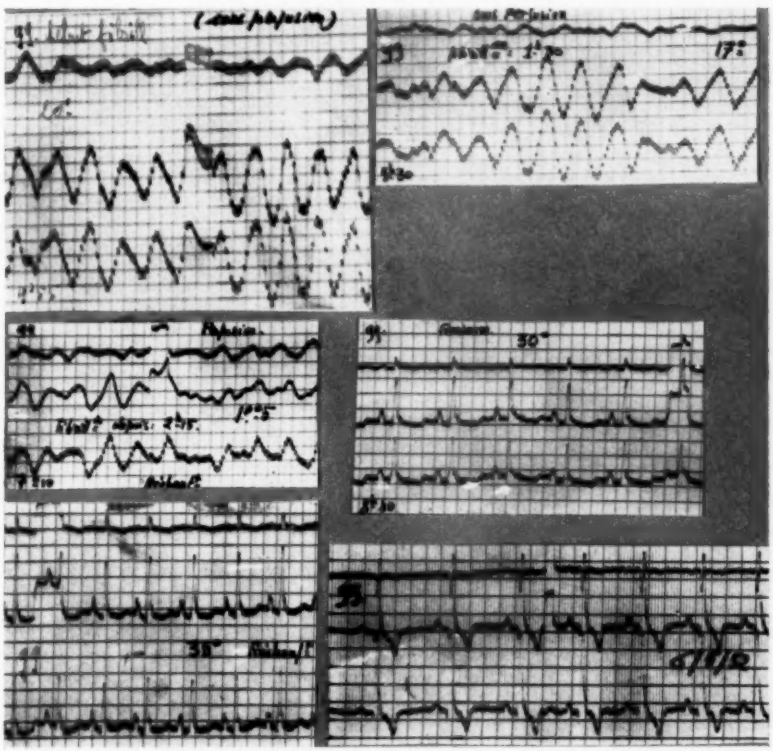


Fig. 10 (Case 99).—*A*, Just at onset of fibrillation. Perfusion started immediately. Notice good fibrillating waves. *B*, Fibrillating since 1 hour and 30 minutes. Notice rhythmic waves during fibrillation. *C*, After 2 hours and 15 minutes, fibrillation. *D*, During rewarming. *E*, 35° C. on rewarming. *F*, 15 days later.

Å. Senning working independently from us in Crafoord's laboratory was the first to provoke deliberately ventricular fibrillation at normal temperature under perfusion. This was done with the idea of obtaining a cardiac standstill during operation and perfusion. Senning has been able to demonstrate at normal temperature that fibrillation is not dangerous per se provided there is proper cardiac oxygenation. He fibrillates the heart and defibrillates it in the open chest. His results are in our opinion quite convincing from a physiologic angle. We are able to confirm entirely his views about the innocuity of ventricular fibrillation, although working in different conditions. The simple fact that we have observed a dog cooled to 12° C., fibrillating 3 hours, and then rewarmed and surviving leaves little doubt about the ability of the heart to withstand severe stress despite fibrillation of long duration. In most instances, we have

allowed the heart to fibrillate for more than two hours, and many times three hours and more (see Tables). This was done in order to ascertain that the machine supports entirely the animal during the fibrillation time. In reality the heart-lung supported the animal for a much longer time, since no artificial respiration has been used from the beginning of fibrillation until return of spontaneous breathing. Table IV gives the time of interruption of respiration in these experiments and offers an idea as to the time during which the machine entirely supported the animal.

TABLE IV. RESPIRATORY FUNCTION IN DOGS DURING EXTRACORPOREAL CIRCULATION WITH LOW BODY TEMPERATURES (INCLUDING NONOPERATED AND OPERATED DOGS)

DOG NO.	ANESTHESIA	COOLING °C. AT WHICH RESPIRATION ARREST NOTED	REWARMING °C. AT WHICH RESPIRATION RETURN NOTED	MINIMUM TIME OF RESPIRATION ARREST (MIN.)	
66	Mem-curare	24	25	50	Perfused with the disk oxygenator
68	Pento-curare	—	22	120	
69	Pento-curare	19.5	20	140	
71	Pento-curare	18	31	215	
72	Pento-curare	30	25	120	
73	Pento-curare	18	dead	—	
74	Pento-curare	—	24	120	
77	Pentothal	—	dead	—	
79	Pentothal	—	—	60	
80	Pentothal	20	26	300	
81a	Pentothal	—	23	190	
82a	Pentothal	—	22.5	180	
83	Pentothal	—	24	105	
87	Pento ether	20	dead	—	
90	Pentothal	—	26	220	
93	Pentothal	23	26	120	Perfused with pair of donated lungs
94	Pentothal	20	24	225	
95	Pentothal	20	22	180	
96	Pentothal	20	21	240	
97	Pentothal	23	21	300	
98	Pentothal	19	dead	—	
99	Pentothal	—	21	180	
102	Pento-ether	21	23	335	
103	Pentothal	21	24.5	315	
105	CO_2-curare	16	17	75	
106	CO_2-N_2O	17	19	135	
107	Pentothal	22	24	215	
108	Pentothal	18	23	190	
109	Pentothal	24	21	335	
75	Pento-curare	—	dead	—	Intracardiac surgery
76	Pentothal	—	dead	—	
82	Pentothal	—	dead	—	
84	Pentothal	—	26	240	
86	Pentothal	22.5	25	200	
100	Pentothal	20	26	390	
101	Pentothal	20	22	290	
104	Pentothal	—	25	300	

An essential point to be observed is that the coronary circulation must be adequate. By this we do not only mean sufficient blood flow but possibly not too great a blood flow.

Inadequacy is seen in the electrocardiogram as waves of low amplitudes. In the very few animals where defibrillation has been impossible we had mechanical troubles with our pumps, and electrocardiographic tracings are convincing of an inadequate coronary blood flow during the whole or long periods of fibrillation (Fig. 11, C, Case 105).

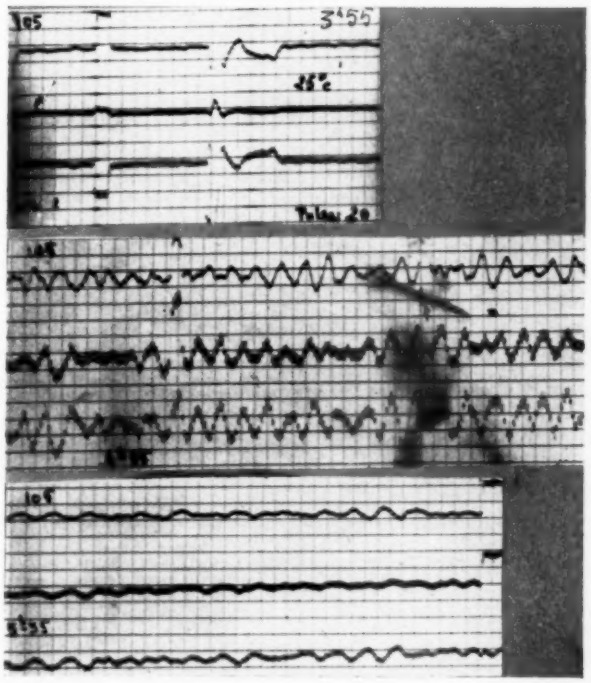


Fig. 11 (Case 105).—Failure to defibrillate due to anoxia during rewarming. *A*, Prior to fibrillation during cooling. *B*, Fibrillation during cooling. *C*, Low voltage waves during fibrillation. It was impossible subsequently to defibrillate this dog in the usual manner.

DEFIBRILLATION

Defibrillation occurred spontaneously in a number of animals (Figs. 3, 7, 12, 13).

During Cooling.—To our surprise we have seen several spontaneous defibrillations during further cooling and perfusion. This seems to point out that in many of the cooling fibrillations this phenomenon is due partly, as Hegnauer and Penrod have pointed out, to coronary inadequacy. These defibrillations were either definitive or lasted for 20 to 30 minutes until further cooling or rewarming reversed the situation to a new fibrillation. During operation we have also noticed several times such spontaneous defibrillations (Case report 101 and Fig. 14).

During Rewarming.—We have seen some spontaneous defibrillations during this time, and also after operation with the heart open. The animal maintained therefrom a normal pulse rate for the temperature considered.

TABLE V. SPONTANEOUS DEFIBRILLATION IN HYPOTHERMIC DOGS UNDER EXTRACORPOREAL CIRCULATION

	DURING COOLING										DURING REWARMING									
DOG NO.	°C. AT FIRST FIBRILLATION	DURATION OF PERFUSION AT FIRST FIBRILLATION	DURATION OF FIRST COOLING DEFIBRILLATION	DURATION OF PERFUSION DURING FIRST PERFUSION	DURATION OF FIRST FIBRILLATION	TEMPERATURE OF SECOND COOLING FIBRILLATION	PULSE RATE JUST BEFORE FIRST FIBRILLATION	BLOOD PRESSURE JUST BEFORE FIRST FIBRILLATION	PULSE RATE PRIOR TO SECOND FIBRILLATION	BLOOD PRESSURE PRIOR TO SECOND FIBRILLATION	LOWEST TEMPERATURE RECORDED	°C. OF FIRST REWARMING FIBRILLATION	BLOOD PRESSURE PRIOR TO FIRST REWARMING FIBRILLATION	PULSE BEFORE	DURATION OF PERFUSION WHEN FIBRILLATES	REWARMING DURATION WHEN FIBRILLATES	°C. OF SECOND FIBRILLATION	SPONTANEOUS DEFIBRILLATION AT	PERFUSION DURATION FROM LAST FIBRILLATION	FIBRILLATION DURATION FROM LAST FIBRILLATION
94	20	0	20	7	77	17		120	16	40	16.5	—	—	—	—	—	—	20	140	140
97	23	0	20	20	25	—	—	?	—	—	15	—	—	—	97	95	19	—	no	no fib.
101	—	—	—	operation intracardiac						—	14.5	16	—	—	10	60	18	18	—	—
103	14	90	—	170	170	—	—	?	—	—	12	—	—	—	—	—	—	16	170	170
108	15.5	0	—	115	115	—	15	80	—	—	15	—	—	—	—	—	—	23	115	115
109	24	0	17	210	225	—	?	90	—	—	14	—	—	—	—	—	—	—	no	fibri.

This is not the place to fully discuss the significance of these phenomena. They simply point out once more the fact that cold produces reversible phenomena in the nonhibernating mammal. This fact permits confidence in the development and further applications of the general method. Figs. 3, 7, 12, 13 and 14 illustrate cases of spontaneous defibrillation, and Table III gives a general view of the defibrillation circumstances.

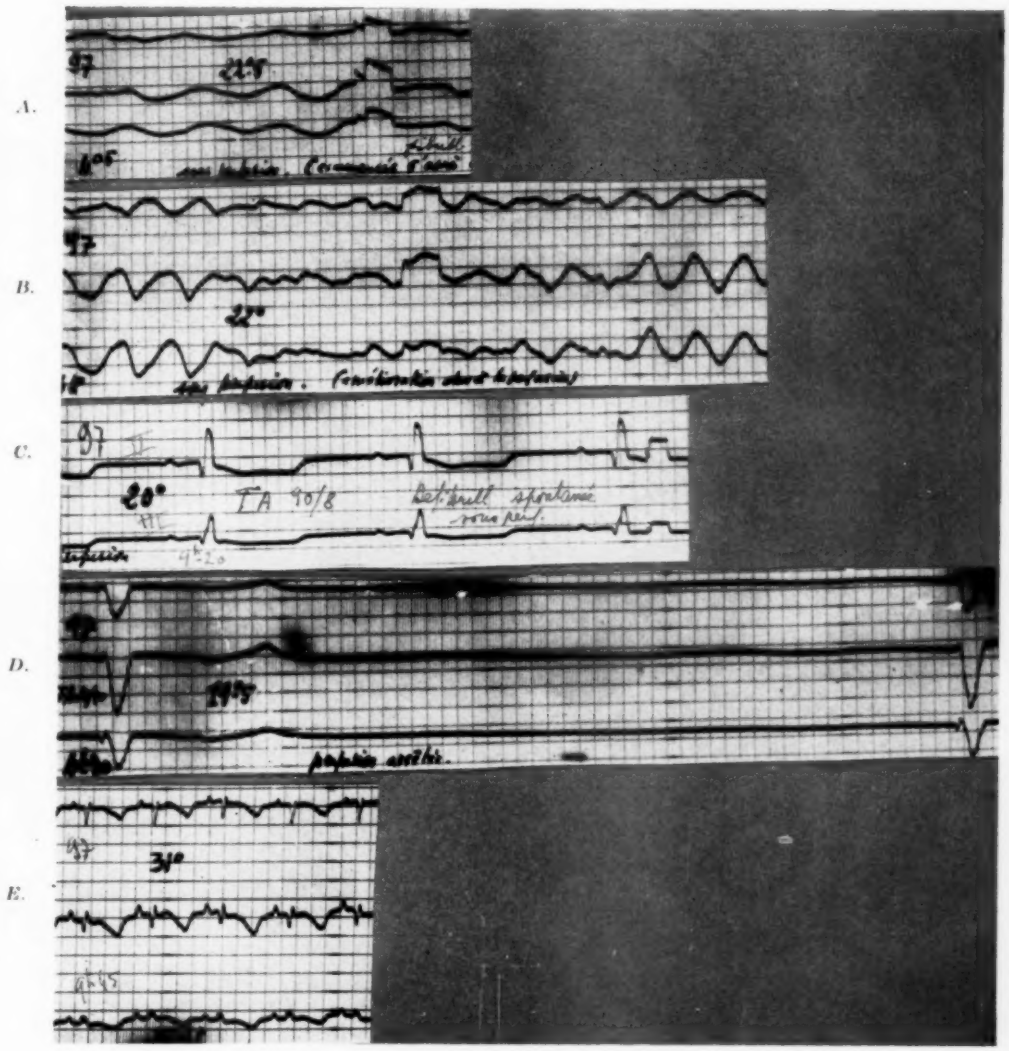


Fig. 12.—Spontaneous defibrillation occurring during cooling. (Fibrillation at 23° C. Delayed perfusion. Defibrillation spontaneous at 20° C.) *A*, Fibrillation just after perfusion was started. Notice waves of low amplitude and slow rate. *B*, After 30 minutes, fibrillating waves have improved considerably. Larger amplitude and faster rate. *C*, Spontaneous defibrillation occurred on further cooling, showing the importance of an adequate coronary blood flow. *D*, When perfusion was stopped, pulse rate decreased. *E*, Dog was rewarmed almost completely (31° C.). Died at 35° C. from cardiovascular collapse.

ELECTRICAL DEFIBRILLATIONS

As can be seen in Table I fibrillation occurred in 33 dogs. In 30 dogs it was necessary to use shocks to defibrillate them (Table III). Except in one operated dog with the disk oxygenator, it was always the case when using this apparatus. With the lung preparation (Fig. 2) we have made it a policy to defibrillate the heart around a body temperature of 20° C. However, we are more and more convinced that with slower rewarming and better use of the pumping mechanisms we will see more of the rewarming spontaneous defibrillation.

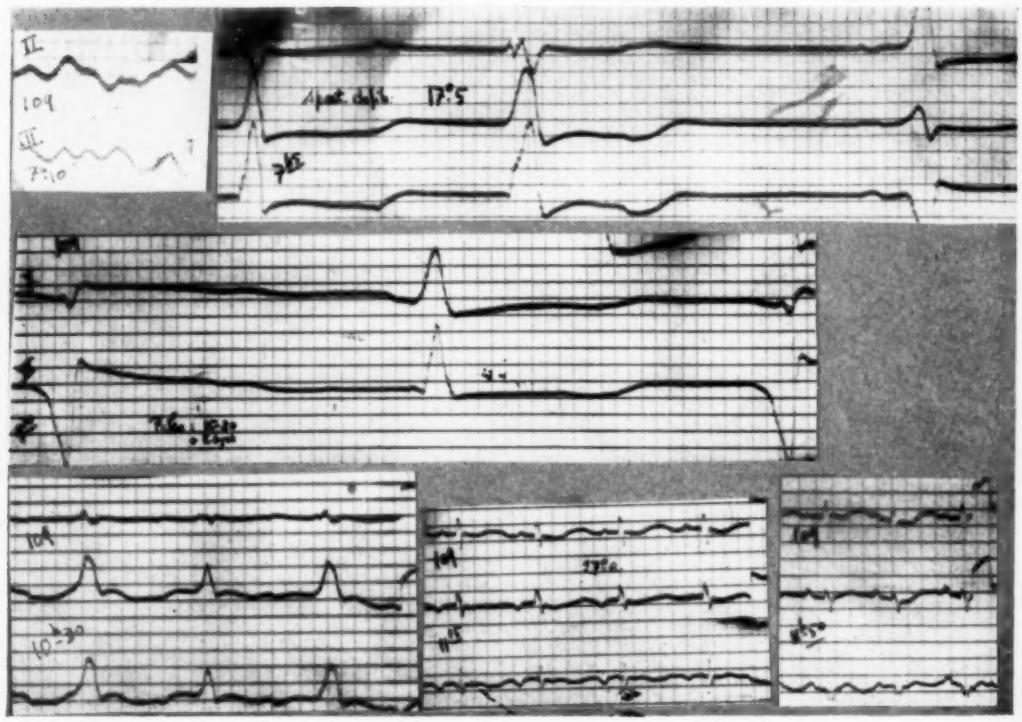


Fig. 13.—A case of extracorporeal circulation combined with hypothermia. *A*, Perfusion was started only 10 to 15 minutes after the onset of fibrillation. *B*, Spontaneous defibrillation on lowering temperature under perfusion, showing influence of proper coronary circulation. *C, D, E, F*, Aspect of electrocardiograms on rewarming.

Defibrillation is accomplished as described. In some cases one single shock is sufficient, in others one or several series are necessary. Many times the defibrillation is only of short duration, and fibrillation sets in again. Shocks permit return to normal beats. Thus fibrillations and defibrillations may be dealt with several times until definitive defibrillation is appearing. We have termed defibrillation in the tables as the definitive reapparition of normal beats. In no case has the death been due to a new fibrillation at high temperature. When we have failed to defibrillate the heart (3 cases) it has always been possible to find out the reason of this failure: air compressor failing during rewarming, leaving the pump with no power, poor perfusion technique, etc. In one case, failure to defibrillate with a shock was followed 3 minutes later by a spontaneous defibrillation (Fig. 7 and Case 108).

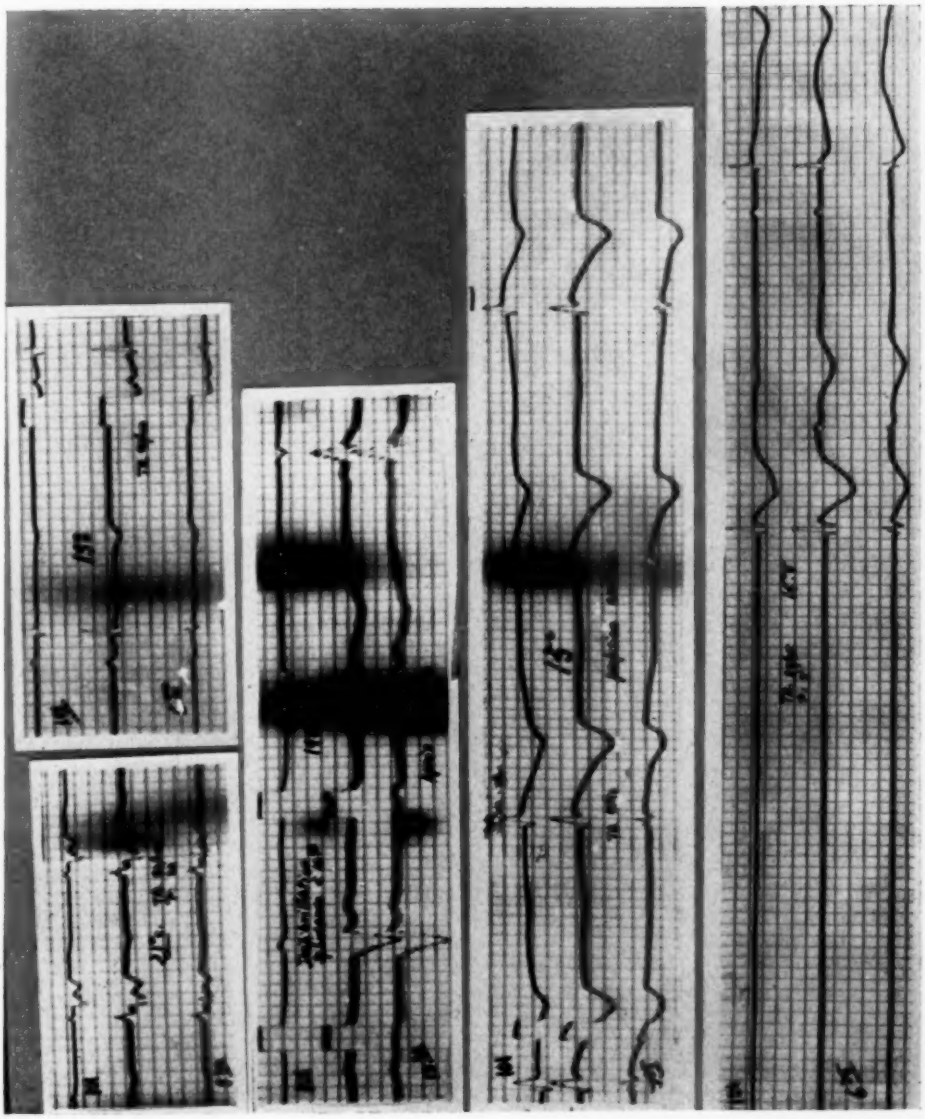


Fig. 14 (Case 101).—Operation (heart open through right ventricle) and spontaneous defibrillation consecutively. *A*, 21° C. cooling. *B*, 19° C. *C*, 16.5° C., Pulse 3 per minute. Perfusion is started. *D*, 15° C., Pulse has gone up to 22 per minute with improved electrocardiogram (more regular) showing influence of improved coronary circulation, *E*. 19° C. on rewarming after operation (right ventricle opened during 50 minutes). Spontaneous defibrillation.

This points out the apparent innocuity of such shocks, although we are not fully convinced about this point of technique. Let us point out again that we consider the problem of defibrillation as entirely solved as far as seen from our angle. No further emphasis is needed as far as possible human applications of this problem. Working at normal temperatures and with different techniques Senning has also arrived at the same conclusion that defibrillation can always be accomplished if the heart has received proper oxygenation during its fibrillating period.

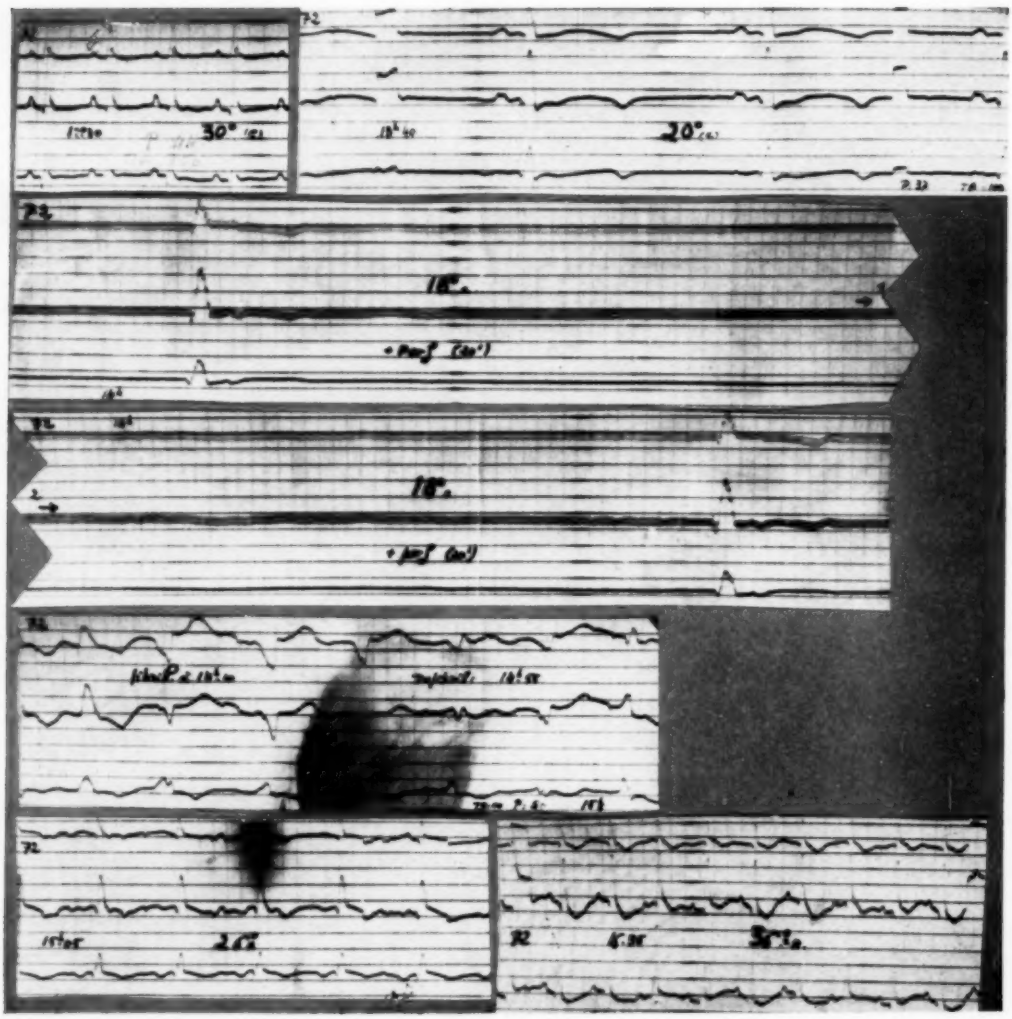


Fig. 15 (Case 72).—Experiment with extracorporeal circulation combined with hypothermia using the Crafoord-Björk apparatus. This is the only animal surviving in this series after prolonged ventricular fibrillation and perfusion. *A* and *B*, Aspects of electrocardiogram during cooling. *C*, Extremely slow pulse even under perfusion. (Note *C* was cut into two parts.) *D*, *E*, *F*, Show aspects of electrocardiogram immediately after defibrillation and during last part of rewarming.

PREVENTION OF FIBRILLATION DURING COOLING AND REWARMING

Recently we attempted to bring the animal to a suitable temperature for operation, maintain him at this temperature for the estimated operating time, and then rewarm him. Using the method described of short serial carotid perfusion of the coronary plus brain perfusion and vein-to-vein perfusion, we have been able to carry out this program satisfactorily. However, the heart fibrillated during rewarming. It was immediately defibrillated, and the animal fully revived. This was done in view of the fact that perfusion during fibrillation toward the coronaries means also sending blood toward the bronchial circulation.

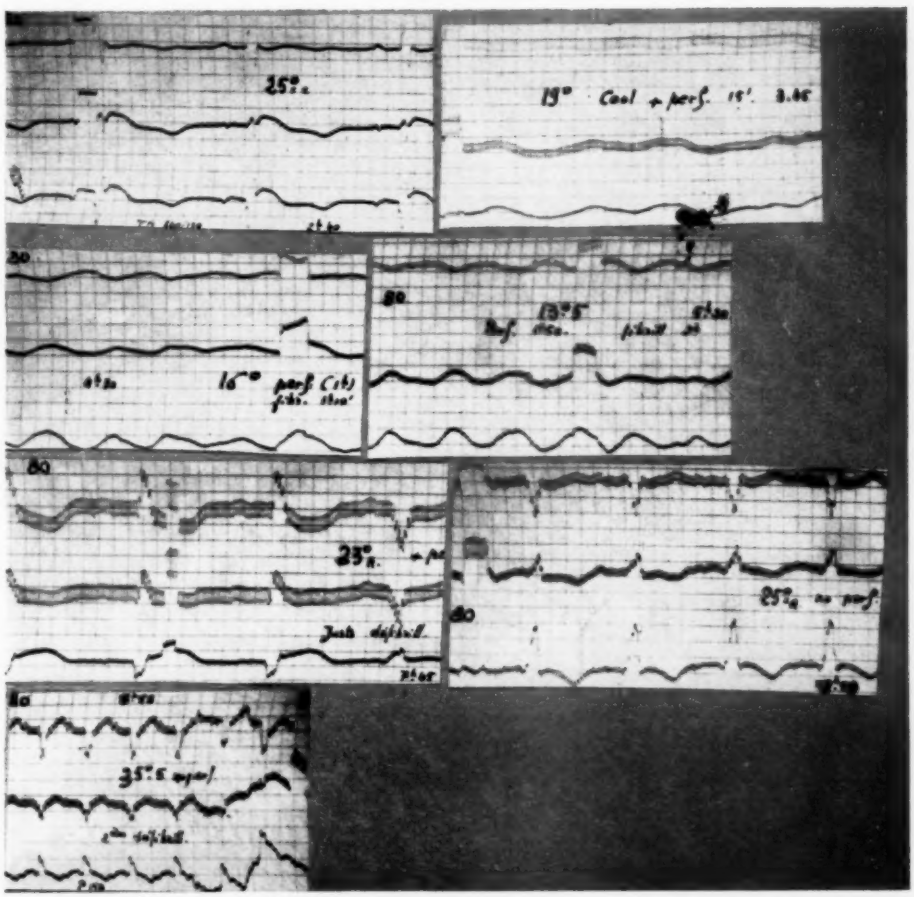


Fig. 16 (Case 80).—*A*, Electrocardiogram at 25° C. *B*, 19° C., fibrillation 15 minutes previously, perfusion on. *C* and *D*, Perfusion on, cooling. *E*, *F*, *G*, Electrocardiogram just after defibrillation and during late rewarming.

Having convinced ourselves of the feasibility of supporting an animal during cardiac arrest, we clearly realized that this was done under none too physiologic conditions. Since the heart is incapable of emptying itself of the blood that may arrive in its left cavities, perfusion of the bronchial arteries in such a state might only lead toward pulmonary hypertension and/or cardiac dilatation. It then

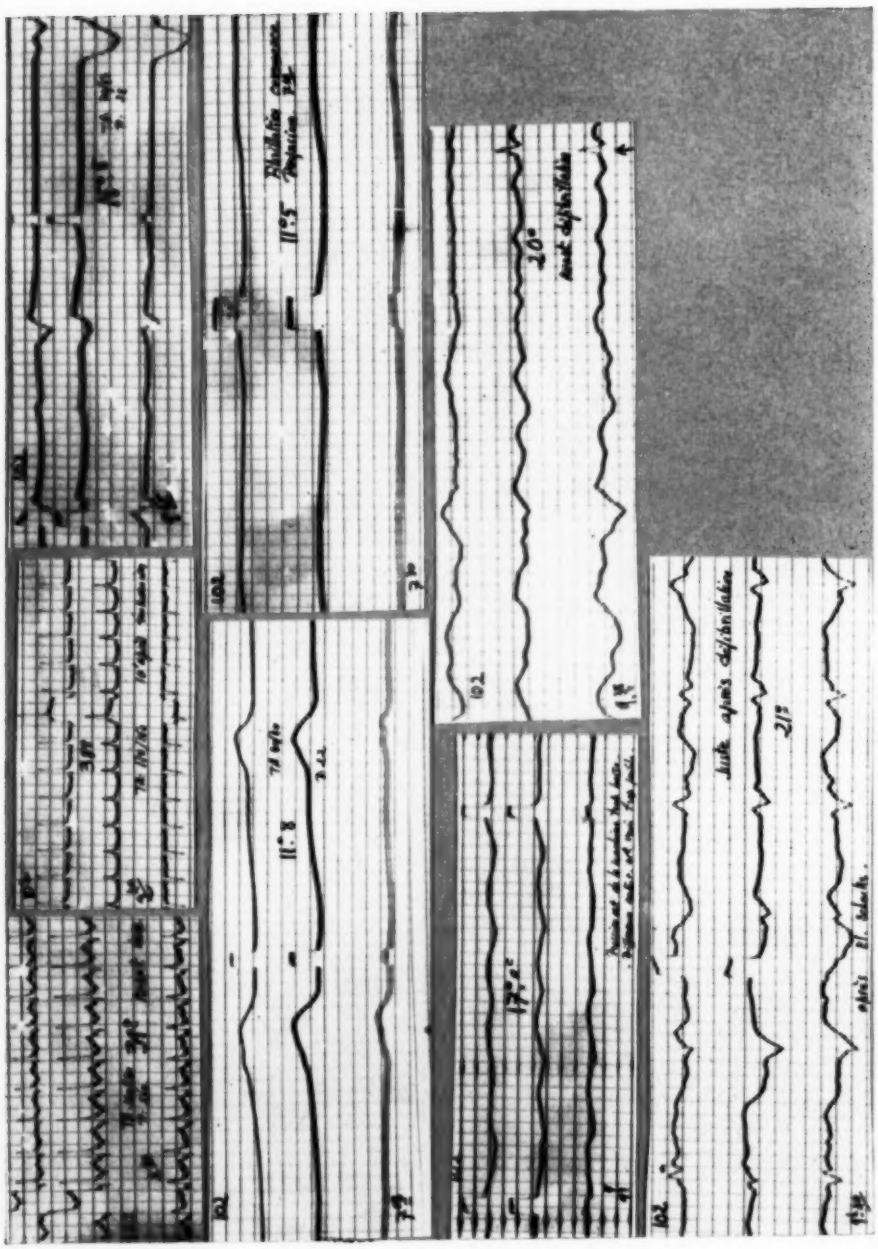


Fig. 17 (Case 102).—See case report. *A*, Just before immersion. *B*, 10 minutes after immersion (notice altered electrocardiogram). In this dog there was a shocklike picture at this stage. This clinical behavior had not been observed in other experiments. *C*, *D*, Before fibrillation at low temperatures. *E*, Fibrillation under perfusion. Notice extremely low amplitude and rate. *F*, *G*, Fibrillating waves none too satisfactory. Notice in *G* at arrow one spontaneous isolated QRS complex (it corresponded to an isolated beat). *H*, Recorded just after defibrillation with electroshocks.

seemed logical to verify if it were possible to work in accordance with an operative schedule. Fibrillation or cardiac standstill might be desirable during operation (in order to prevent air embolism) but not before. To be able to bring a patient to the necessary temperature it is desirable to avoid fibrillation until proper cardiac drainage can be established at operation. Apparently this program is feasible. The reason for the rewarming fibrillations has not been clarified. We believe that oxygen deficiency is the cause, although we cannot prove it at present.

REWARMING SURVIVALS AND DEATHS

It may seem paradoxical to say that there was little noticeable difference between the animals that survived and those that died. During rewarming the life processes return and follow mainly the pattern indicated by Bigelow. Respiration returns (see Table IV) and reflexes reappear. In the cases treated with Crafoord-Björk oxygenator we never noticed signs of wakening or approaching consciousness. The contrary is seen with the other method. This we believe is due to better perfusion technique in the latter cases, as well as to better anesthesia.

Difficulties During Rewarming.—When the temperature approaches 26° or 27° C. the dogs showed in many instances signs of anoxia and, later, difficulties in venous return. It is worthwhile mentioning that with the exception of a few dogs, the late rewarming period has been difficult. The dogs, it seemed, could not fix oxygen properly. This was the case in the dogs who died as well as in those who survived. Whether this was due to the fact that we did not inflate the lungs during perfusion or to the destruction of some respiratory enzymes necessary for proper hematosis (as suggested by A. Thomas) we are not prepared to say. In any case it has seemed to us that when O_2 was difficult to fix, an infusion of a 30 per cent glucose solution would improve the situation at least temporarily.

Donated Lungs.—As others have pointed out, donated lungs are usable during an unpredictable period at high temperature. Edema renders them unusable after a short time. At low temperatures this has never been a factor, except for one dog where we used a lung, preserved for 48 hours, which was unusable after fifty minutes. We could properly oxygenate the small amount of blood that is necessary for several hours. When edema appears, it is never a nuisance.

Minute Blood Flow.—The minute blood flow has been located around 200 c.c. per minute at 16° to 20° C. In view of the small difference in arteriovenous saturation this may have been too large an amount. Surviving dogs of 20 kg. have been supported with blood flow ranging from 150 to 180 c.c. per minute according to the temperature. Needless to say this increases during rewarming. At this time, however, the machine is only an additional help to the animal as its heart and lungs are doing most of the work. Such a reduction in minute blood flow approaching a twentieth of the normal is probably the greatest advantage of this method. Procedures for adjusting automatically the blood flow to the arteriovenous difference are under construction, as well as an automatically regulated system of several pumps.

We came to the conclusion that all our variables in the machine must act automatically and follow the patterns given by the variable "milieu interieur" of the body. We are dealing here with an action of the body on the machine and conversely, an action of the machine upon the body mechanisms. Accordingly we are developing methods of electronic controls to provide for such actions and reactions.

Operations.—In this series all the animals died either during or after operation (our survivors' series will be published at a later date).

This we do not consider as indicative of the value of the offered method, since most of these operations were performed at the start of our experience, with inadequate means and were mostly due to avoidable accidents such as slipping of cannulas, air bubbles from an inadequately prepared and adjusted filter, postoperative hemorrhage with no blood at hand, etc. On the other hand we did not attempt to perfect the operative procedure. We considered that it was first necessary to develop an adequate perfusion method. We believe our second step should be the appraisal and use of a convenient and reduced artificial lung. In man, it may even prove feasible to use a fresh human lung or a part of a lung for operation. It remains to be seen if a properly washed lung donated by another mammal cannot be used for such purpose.

Fig. 18.—Pathologic findings in Case 102, petechias over the endocardium.

In any case this series of operations has proved to us: (1) that the method permits a satisfactory exposure of the heart, with a reduced coronary blood flow; (2) that fibrillation during cardiac operation is desirable, as Senning has pointed out; (3) that defibrillation after operation (an incision in the heart 5 cm. long) is possible either with the opened or closed chest. In one case spontaneous defibrillation appeared at 18.5° C. during rewarming after operation. (Case Report 108).

Deaths.—Many of our deaths have been due to pulmonary atelectasis. We have also had delayed deaths after 10 to 24 hours (48 hours in one case). Cerebral

damage must not be overlooked as a cause, either due to perfusion difficulty especially during rewarming when working with an inadequate pump or secondary to prolonged anoxia due to atelectasis or both. All the survivors have had a degree of coughing pointing to pulmonary complications. More details about these deaths will appear later.

Pathology.—No factors due to cold per se have been noticed after early death. In some cases small petechiae under the endocardial surface were seen. They may be related to heparinization. In any case they seem of no clinical importance. We have made the same observations after sacrificing a noncooled dog. They may emphasize a special capillary fragility in cold (Fig. 18).

One dog had a bundle branch block (Fig. 10). This may have been due to: (1) excess in coronary blood flow leading to bleeding in the presence of high heparinization; (2) action of cold; (3) small clot from perfusion technique. This dog is normal otherwise. At autopsy one dog had still some signs of atelectasis 2 months after cooling and prolonged fibrillation. On the other hand the myocardium showed signs that might be interpreted as due to parasitosis or a myocarditis. Its behavior was entirely normal with full activity. One dog was sacrificed after 15 days because of a large burn on the chest due to rewarming lamp. There were no other signs of pathology at autopsy (Case 103).

POSTOPERATIVE DAYS

All the dogs were either temporarily blind or paralyzed in the hind legs the day following the experiment. This we have shown is due to fixation of barbiturates, with retarded elimination. One dog after cooling to 12° C. still had 1 mg. per cent of barbiturate in the urine 5 days after operation (Case 103, Fig. 3). It seems that the greater the cooling the longer is the time of elimination, in the absence of any liver or renal disturbance. It has recently been shown that barbiturates are fixed in the motor part of the lumbar spine. It is also a common observation that the first symptom observed after intraperitioneal Nembutal is weakness of the hind legs. It is an open question whether the drug is fixed in the nerve cell or if its metabolism is changed during cold. Personally we favor the first hypothesis. In any case all symptoms cleared after the second or third day. Electroencephalograms were normal in all dogs after survival.

DISCUSSION

We realize that the results presented here are no better than those offered by any conventional method of perfusion. We have confidence, however, in the future of hypothermia in problems interesting the cardiac surgeons. However, hypothermia is still a new field. It has inspired in the past such a horror to traditional medical thinking that it may be necessary to point out several facts that we have not been able to make stand out in the preceding pages.

I. *Reduction in Body Temperature and Its Inconvenience.*—We would emphasize the main drawbacks that are clearly seen at present rather than pointing out the advantages which, we believe, stand for themselves. Among the disadvantages are:

A. The necessity of having at hand a perfusion technique permitting long perfusions. However, it is possible that the use of moderately low temperature in man, such as 25° to 20° C., will render this point less important. As far as we are concerned we think that a reduction lower

than 25° C. is necessary. Should this prove to be the case, the perfusion must be available at once in case of fibrillation. It must be appreciated that under operating conditions the perfusion may have to last during the whole operation and sometimes after its completion.

B. Possible damaging effects of deep hypothermia may be considered. Although we are convinced that such damage, if present, is of minor importance, it must be emphasized that many aspects of the behavior in cold and rewarming remain to be clarified. It is the task of those interested in this field to find the proper answer for each of these. Examples of the patients treated by Talbott, Smith, and Fay and others are encouraging so far as this is concerned. More knowledge must be gained from the mechanisms of fibrillation in the nonhibernating mammal. It is not understood why the hibernator can maintain constant his neurovegetative automatisms while the nonhibernator cannot. We are not convinced of the ability of a damaged heart to withstand our method or of its abilities to withstand other kinds of aggression. Experience alone will answer this point. The example of cooled patients to the temperature range of 24° to 25° C. is however reassuring in this respect.

C. The dangerous effects of rewarming are considered. Rewarming deaths have been observed by all after simple cooling, but like others we can only theorize about these mechanisms. Our explanation lies in the possibilities of damage to the vasomotor centers during cooling, and to the stress effect of rewarming. In the hibernator Suomalainen from Helsingfors has found the so-called signs of stress during rewarming. It would indeed be very interesting to know the incidence of rewarming death among these presumably adapted animals. We have in these experiments rewarmed the animal as quickly as feasible and with no special precautions. It is possible that in the future rewarming must be accomplished more cautiously. On the other hand rewarming might not need be complete. No precautions were taken in view of the facts that:

1. Each of these experiments lasted as described from 13 to 19 consecutive hours. 2. We are dealing with healthy dogs. 3. We are interested in not complicating a rather elaborate experimental scheme.

We have been able to control the deaths due to rewarming and our deaths must be considered as pertaining to the difficulties of this perfusion technique. Rewarming deaths, whatever the causes, are due to cardiac fibrillation or acute failure. We have seen that this can be overcome. On the other hand some ideas about the necessary means of protection that such people should receive are appearing in the light of the present study of hypothermia.

CONCLUSIONS

It is possible in dogs to lower the body temperature to levels ranging from 12° to 16° C. to replace the circulation by a simple perfusion method during ventricular fibrillation exceeding three hours, to control this fibrillation through the unopened chest, and to have the animal return to normal life.

It is possible to use the same technique for intracardiac surgery within desirable time limits.

Further technical developments are highly needed, in view of human applications.

ADDENDUM

Since this paper was written (April to August, 1952) we have started with human applications in association with our chief: Olivier Monod. Results will be published later.

REFERENCES

An extensive bibliography on the subject of hypothermia has been published with our article in La Presse Médicale in August, 1952. We deem it inadvisable to reproduce it here since it may be consulted at length in this publication.

On the other hand, a few articles dealing with the same subject have been published since this article was written (April, 1952), but we feel that since this work has been original we need not refer to published papers after the publication in La Presse Médicale.

APPENDIX

EXPERIMENTAL CASE REPORTS

Control dog: Perfusion at normal body temperature
Oxygenator: Disks (saline in apparatus)

Dog 64, Male, 9 kg.

Time*	B. P.	Pulse	Observations
0			Usual preparation (see text).
2:00	140		Perfusion starts.
2:02	0		As soon as perfusion started, B.P. dropped to zero. Noradrenaline infusion drip-by-drip brings pressure back to 140.
2:45	140	50	Urine emission. B.P. very unsteady (140 to 150). There is a large portion of the blood volume constantly substracted and inadequately returned.
2:50			Death.

Cause of death: Hemorrhagic shock.

Extracorporeal circulation combined with hypothermia
Oxygenator: Disks

Dog 69, Female, 20 kg.

Time	B.P.	Pulse	Temp.	Observations
0				Usual preparation.
2:05	170		37	Immersion. Curare 5 mg.
4:15	140		21	Perfusion started.
4:40			19.5	Perfusion stopped due to mechanical troubles.
5:15	80	2	18	Perfusion starts again. Respiration stopped.
6:30	40			Blood in machine = 130 c.c.
7:10			18	Ventricular fibrillation.
7:30			17.5	Rewarming starts.
8:00			20	Defibrillation. 4 electroshocks, 220 v. 6 a. Respiration returns.
9:16	130		30.5	Perfusion stopped after several attempts to stop it before. (Could not be done due to cardiac irregularities.)
10:05	150		36	Blood from machine given back. Dog is shivering. Back to cage.
25:00				Found dead in cage. Nothing of value found at autopsy.

Extracorporeal circulation combined with hypothermia
Oxygenator: Disks

Dog 72, Female, 13.5 kg. (Fig. 15)

Time	B.P.	Pulse	Temp.	Observations
0				Usual preparation.
2:00	150	140	35	Immersion.
3:25	100	44	20	Perfusion started (into carotid artery).
3:55		8	18	Ventricular fibrillation.
4:10	110		17	Noradrenaline drip. Rewarming started.
4:35			24	Defibrillation. 2 shocks, 200 v. Perfusion stopped.
4:40	110		25	Spontaneous breathing returns.
4:41	20/30			Perfusion started again because of low B.P.
4:50	130/120	90	27	Perfusion stopped. Notice good pulse rate.
6:10	100	160	37	All reflexes present. Back to cage.

19:00.—Dog in good condition but still unconscious. Does not see, does not move hind legs.
5 days.—Entirely normal. Plays, jumps, friendly as before.
21 days.—Dog was killed by accident by other workers. Nothing abnormal was found at autopsy.

*All time is expressed in hours and minutes after 0 time.

Extracorporeal circulation combined with hypothermia
Oxygenator: Disks

Dog 74, Female, 20 kg. (Fig. 6)

Time	B.P.	Pulse	Temp.	Observations
00				Usual preparation.
2:00	110			Immersion.
3:00	110	60	24	Ascorbic acid, 0.5 Gm. (Fig. 6,*A*).
3:30	110	42	20	(See Fig. 6,*B*).
4:30			15	Ventricular fibrillation, perfusion starts (Fig. 6,*E*).
5:25			19	After 58 minutes fibrillation under perfusion (Fig. 6,*F*).
5:40			22.5	Defibrillation with a series of extrathoracic electroshocks (Fig. 6,*G*).

Dog was fully revived to 37°C. Died 12 hours later.

Extracorporeal circulation combined with hypothermia
Oxygenator: Disks

Dog 80, Female, 15 kg. (Fig. 16)

Time	B.P.	Pulse	Temp.	Observations
0				Usual preparation.
1:50	140		35.5	Immersion.
3:20			20	Ventricular fibrillation. Perfusion starts with a few minutes delay due to lack of ready connections with machine.
6:40			13	Rewarming started.
7:00			14.5	Muscular fibrillation observed at tongue edge.
7:20			18	Picrotoxin, 2.6 mg. in artery.
7:45	20/15		23	Defibrillation. 2 electroshocks, 250 v. 7 a. Fibrillated and was defibrillated with one shock at four different times.
8:15	140		27	Spontaneous breathing. Perfusion stopped.
8:35	180	160		Rise in B.P. may have been due to delayed appearance of Noradrenaline in blood or/and to cerebral damage. Pulse rate passed from 60 to 160 at a body temperature of 32° C. in an abrupt manner (trigger-like).
9:00	130	160	37	Good respiration. Signs of wakening. One ml. Nembutal was inadvertently given intravenously, and at once fall in B.P. and death, despite attempts with Noradrenaline.

Extracorporeal circulation combined with hypothermia
Oxygenator: Disks

Dog 83, Female, 22 kg.

Time	B.P.	Pulse	Temp.	Observations
0				Usual preparation.
3:00	165	120	37.5	Immersion.
6:30	70		16.5	Ventricular fibrillation. Perfusion starts. Rewarming.
7:50			22	Defibrillation, one shock, 260 v. 4 a. Large hemorrhage during transport due to cannula slipping. No blood at hand to replace blood loss.
8:15	170		24	Perfusion stopped. Spontaneous breathing.
8:35	130	110	28	Perfusion Noradrenaline stopped.
9:00	130	120	36	Everything O.K., good breathing. Back to cage.
22				Found dead in cage. No important findings at autopsy.

Control dog: Perfusion at normal body temperature
Oxygenator: Disk oxygenator

Dog 85, Male, 17 kg.

Time	B.P.	Pulse	Temp.	Observations
0				Usual preparation (see text).
1:20	175/170			Vessel catheterization finished.
2:50	180			Perfusion starts: Min. blood flow = 300 c.c.
2:55	90			Notice drop in B.P.
5:40	105		29	B.P. unsteady.
6:54	160			Perfusion stopped. Almost all blood from machine given back to dog.
8:50				Stepping motions of anterior legs. Waking up.

24 hours.—Still in same posture as when left day before. Rapid shallow respiration. Feels pain. No cortical functions.
48 hours.—Still lying on side. Unconscious. Does not see or hear.
3 days.—Reacts to strong noises. Eats and drinks. Reacts to tickling.
9 days.—Slow but complete recovery. On fifth day was very angry and tried to bite. Is now again very friendly and playing with mates and keepers.
One month.—Sacrificed. All normal. Lungs used to oxygenate dog in experiment 93.

Control dog: Perfusion at normal body temperature
Oxygenator: Disks (saline in apparatus)

Dog 88, Male, 12 kg.

Time	B.P.	Pulse	Temp.	Observations
0				Usual preparation.
1:45	180	140	37	Surgery over.
1:55				Perfusion started with saline solution. No drop in B.P. seen at first. Drop to 140, however, when return blood flow to machine increases somewhat.
2:05	110	140		Machine rate very slow (about 100 c.c. per minute), however, note drop in B.P.
4:45	60			Blood pressure unsteady, dropping constantly despite considerable amount of Noradrenaline. Dog seems awake but unconscious.
5:00				Perfusion stopped. On reinjecting blood from machine B.P. came back to preperfusion level. Hemolysis negligible after a 3-hour perfusion.
8:00				B.P. still dropping. Noradrenaline obtains temporary improvement. Respiration deep and slow. Dog is seen twice having forced extension of 4 legs as well as back and head (Convulsion?)
8:10				Died soon after returning to cage. Respiratory arrest actually observed. Cardiac arrest 5 minutes later.

Autopsy.—Nothing of value. Brain not examined. Spleen retracted, very small. No edema in lungs, heart normal. Hemorrhagic shock.

Control dog: Perfusion with normal temperature
Oxygenator: Disk oxygenator

Dog 89, Female, 12 kg.

Time	B.P.	Pulse	Observations
0			Preparation as usual.
2:10	140		Perfusion started. First drop in B.P. was observed. Careful adjustment of fluids and minute blood flow obtains adequate maintenance of B.P.
2:45			Dog shivering. B.P. unsteady. Min. blood flow 300 c.c.

3:15		Loss of feces. Breathing minimal.
4:00	110	Hematocrit 25 per cent. Hemolysis nihil.
5:30	150	Perfusion s opped.
7:30	50	After progressive B.P. drop, dog showed some degree of anoxia and acute pulmonary edema resulting in death.

Extracorporeal circulation combined with hypothermia
Oxygenator: Donated lungs

Dog 94, Male, 15 kg. (Fig. 9)

Time	B.P.	Pulse	Temp.	Observations
0				Usual preparation.
1:25	180	112	39	Immersion. (Dog 94a killed by hemorrhage. Lungs taken and connected.)
3:00	120	76	25	Heparin, 50 mg. Insulin, 20 units.
4:00			20	Anoxia due to respiratory arrest which was overlooked. Ventricular fibrillation (Fig. 9, C). Perfusion on.
4:07	90			Spontaneous defibrillation (Fig. 9,D) with proper B.P. Perfusion off.
4:21	60	40	19	Heart very irregular. Large drops in B.P. 20 units insulin with 200 c.c. 10 per cent glucose.
4:30	50	30	18	Heart regular (Fig. 9,E)
5:04			17	Ventricular fibrillation. Perfusion on again (Fig. 9,F).
6:35			17	O_2 analyses in vein and artery (Van Slyke)

	CO_2	O_2 vol.	O_2 cap.	O_2 sat.
art.	25.2	22.6	22.7	99.8 per cent
vein	32.1	15.6	22.6	68.9 per cent

6:55			16.5	Dog, slightly hypoxic.
7:25	80	68	20	Spontaneous defibrillation (Fig. 9,G).
9:25	170	135	35	(Fig. 9,H) Reacts to pain. B.P. steady. Heart O.K.
10:00			36	Back to cage, almost awake.

April 8.—(24 hours later). Dog all right. Seems a little "shy." Tries to walk. Still under barbiturates.
April 10.—Plays and jumps. Quite normal.
May 5.—Electroencephalogram normal in every respect.

Extracorporeal circulation combined with hypothermia
Oxygenator: Donated lungs

Dog 97, Male, 14 kg. (Fig. 12)

Time	B.P.	Pulse	Temp.	Observations
0		100		Usual preparation.
2:25	155	120	37	Immersion.
3:55			23	Respiratory arrest, followed 5 minutes later by ventricular fibrillation.
4:00				Perfusion started with 400 c.c. blood from donor. Electrocardiogram, Fig. 12,A. Min./blood/flow = 200 c.c./min.
4:10			22	Fibrillation waves improving (Fig. 12,B).
4:20	90	40	20	Spontaneous defibrillation (Fig. 12,C.).
4:30				Perfusion stopped, pulse slowing (Fig. 12,D).
5:10			18	Perfusion on again because of cardiac pauses and extrasystoles.
6:08			15	Perfusion on. 200 c.c./min. Rewarming starts.
7:45			19.5	Ventricular fibrillation. Min./bl. flow = 140 c.c.
8:50			20	Defibrillation with electroshocks.
8:52				Fibrillates again.

8:57			Defibrillation (electroshocks), 240 v. 3.a.
9:50		31	Perfusion stopped (Fig. 12,E).
10:50		35	Blood pressure very unsteady. Picture of shock. Repeated periods of marked anoxia with blue tongue. Finally death. It was in this case the impression that oxygen could not be transported normally by hemoglobin.

Extracorporeal circulation combined with hypothermia
Oxygenator: Donated lungs

Dog 99, Male, 19 kg. (Fig. 10)

Time	B.P.	Pulse	Temp.	Observations
0				Usual preparation.
2:10	170	100	37	Immersion.
4:55	140	32	20	
4:56	0	0	20	Ventricular fibrillation (Fig. 10, A). Perfusion starts. Ph. (in blood) 7.26; Hematocrit: 60 per cent.
5:10			18.5	Min. blood flow, 180 c.c.
5:30			17	Fig. 10, B. Very satisfactory fibrillation.
6:45			14.5	Rewarming starts. Hemolysis: 350 mg.
7:30			21	Defibrillation. 3 series of shocks (10 shocks), 310 v., 3 to 5 a. Respiration comes back almost immediately.
7:40	170	60	25	Notice high blood pressure, due to Noradrenaline injected just prior to defibrillation.
8:10			28	Despite high blood pressure, pulse pressure low and weak. Cedilanid 2 ml. plus ouabain, Aminophylline 5 c.c.; procaine intravenously 1 per cent, 3 c.c.
8:50	140		30.5	Heart regular. Eye reflexes plus. Respiration good. Reacts on pinching (Fig. 10, D).
10:15			37	Dog in good condition. Drip 10 per cent glucose set in. Dog lifts head. Lungs used for oxygenation in perfect condition.

Following day.—Still sleeping but fine.
48 hours.—Friendly but sleepy. Does not see. Hind legs paralyzed.
Fourth day.—Can walk. Can see. Drinks, eats normally.
15 days.—Completely normal. Bundle branch block (Fig. 10, E). Belongs to assisting nurse who has adopted dog. Tenth month.—This hunting dog is now entirely normal in every respect.

Extracorporeal circulation combined with hypothermia
Cardiotomy (right ventricle)
Oxygenator: Donated lungs

Dog 101, Male, 10 kg. (Fig. 14)

Time	B.P.	Pulse	Temp.	Observations
0				Usual preparation.
4:10	130		37	Immersion.
6:00	50		19	Artificial respiration since 5:30.
6:45	35	3	16.5	Perfusion on (slow pulse).
7:03	55	22	15	Perfusion stopped (pulse restored).
7:25			14.5	Operation starts. No fibrillation.
8:20				Temporary closure of vena cava.
8:30				Ventricular fibrillation.
8:33			16	Spontaneous defibrillation (actually observed). Right ventricle opened. Ventricular fibrillation again during 4 minutes, followed again by defibrillation, spontaneous.

9:30			Heart is closed (open 50 minutes).
9:35			Fibrillation.
10:10		18	Spontaneous defibrillation (Fig. 14, E).
10:50	40		Perfusion stopped. Normal beats. Shortly after perfusion was stopped, cannulas slipped from both femoral and jugular vein. It was then impossible to give support to the heart during rewarming. Death ensued.

Operative report.—Large incision parallel to heart base. Good access to valve and lower part of interventricular septum. Coronary bleeding minimal. Much reduced during fibrillation.

Extracorporeal circulation combined with hypothermia
Oxygenator: Donated lungs

Dog 102, Male, 32 kg. (Fig. 18)

Time	B.P.	Pulse	Temp.	Observations
				Two days before experiment was put asleep for clipping. Next day cannot walk or see. Next day normal.
0				Preparation as usual plus ether anesthesia.
2:30	170	220	39	Immersion.
2:55	70			Anesthesia quite light. Shocklike picture, never observed previously.
3:00	40/20			Noradrenaline plus artificial respiration. Cedilanid plus ouabain (see electrocardiogram).
3:30	140/130		28	Blood pressure maintained with Noradrenaline.
6:58	40		12	Heart regular.
7:30			11.5	Ventricular fibrillation. Perfusion starts (3 minute delay). Min. blood flow: 100 c.c.
8:08			10	Rewarming starts.
9:00			16	Noradrenaline started. Min. blood flow too large (bright red venous blood) adjusted to 200 c.c.
9:30			21	Defibrillation. (Several series of electroshocks).
9:55			23	Spontaneous respiration and myosis.
11:55	140/130	160	35	Reflexes returned.
12:25	110		37	Blood pressure unsteady. Râles in lungs. Acute heart failure?
14:00	0	0		Sudden death, last agony respiratory motions seen 3 to 4 minutes later.

Autopsy.—Atelectasis of lungs. Petechias in subendocardium, similar to those described by Hegnauer and Penrod.

Extracorporeal circulation combined with hypothermia
Oxygenator: Donated lungs

Dog 103, Female, 15.6 kg. (Fig. 3)

Time	B.P.	Pulse	Temp.	Observations
0				Usual preparation (Nembutal plus antihistamine).
2:30	150		34	Immersion.
5:10	20		19	Cardiac standstill. Perfusion on for some minutes bringing good normal beats (Fig. 3, C, D).
5:40			18	Cardiac standstill, with perfusion apparatus blood is sent through jugular vein toward right heart. Normal beats reappear (arterialized blood was sent).
5:47				Perfusion though carotid artery on.
5:50	50		17	Artificial respiration stopped. Perfusion on.
6:40	30		14	Minute blood flow = 100 c.c.
7:10			13.5	Ventricular fibrillation (after 5 minutes arrest of machine) (Fig. 3, E, F).

8:10			13	Perfusion stopped for some minutes (6–7). Lungs oxygenating, blood working very satisfactorily with almost no edema.
8:50			12	Rewarming starts.
9:20			12	Rewarming continues.
10:00			16	Spontaneous defibrillation (Fig. 3, G). Cedilanid 0.2 mg. plus ouabain 0.5 c.c. Aminophylline, 2 c.c.
10:35	40	48	20	Fibrillation again (Fig. 3, J). One electroshock, 260 v. 3a., defibrillation (K).
10:55	90	76	24.5	Spontaneous breathing. Pulse regular. Palpebral reflexes, +.
12:10	140	160	32	Reacts very much to pain.
12:40	140	160	35	Sudden drop in B.P. After this B.P. is restored but falls again on transporting dog from warm bath to table.
15:30	100			Various drugs are given including vitamins intravenously, procaine, and insulin plus glucose solution. B.P. is still very unsteady.

Following days.—Dog has made a slow recovery. 10 days after this experiment it is normal, with adequate playing activity. Drinks and eats normally.

However, during rewarming his side was deeply burned by a warming lamp over a surface 20 x 20 cm. This being a small dog, we were forced to sacrifice him on the fifteenth day. See electrocardiogram before sacrifice (Fig. 3, K).

Extracorporeal circulation combined with hypothermia
Oxygenator: Donated lungs

Dog 105, Male, 23 kg. (Fig. 11)

Time	B.P.	Pulse	Temp.	Observations
0				Usual preparation. Curare only to prevent shivering with no further barbiturates given. CO_2, 25 per cent.
2:40	170		37	Immersion.
3:55	80		25	40 units insulin plus glucose 10 per cent, 300 c.c. (Fig. 11, A).
4:20			24	Ventricular fibrillation (Fig. 11, B). Perfusion started with about 4 minutes delay. Spontaneous breathing.
5:35			18	Low voltages in fibrillation waves (Fig. 11, C).
6:20			16	Respiration stops. Min. blood flow 300 c.c. (too high).
7:35			17	Rewarming started. Dog has swimming motions. Seems to approach consciousness (compare with barbiturates for anesthetized dogs).
8:00			20	Several electroshocks fail to defibrillate, same thing repeated at 22° C., failed as well.

It is the clinical impression that this animal had one-half anoxia during rewarming due to inadequate return of blood flow. Defibrillation was thus impossible.

Extracorporeal circulation combined with hypothermia
Oxygenator: Donated lungs

Dog 108, Female, 19 kg. (Fig. 7)

Time	B.P.	Pulse	Temp.	Observations
0				Usual preparation.
4:30	180	200	36	Immersion.
8:15	70	26	19	Still spontaneous respiration. (Respiratory motion stopped 5 minutes later.)
10:00		0	15.5	Ventricular fibrillation.
10:45			15	Marked anoxia during 10 minutes (perfusion no good). Excellent fibrillation now.
11:20			16.5	Rewarming starts.
11:40			20.5	One electroshock, fails to defibrillate (300 v. 5 a.).

11:55			23	Spontaneous defibrillation (Fig. 7, H), 5 minutes later spontaneous respiration returns.
12:30	145	148	30.5	Dog approaching consciousness; reacts to everything.
13:30	150		35	No difficulties whatever with this dog. Every life process returned to normal quite nicely without any help other than rewarming.

Next day.—Hind legs paralyzed. Drinks, although still under barbiturate after effects.
Fifth day.—Entirely normal in every respect. Plays and jumps, friendly as before.

Extracorporeal circulation combined with hypothermia
Oxygenator: Donated lungs

Dog 109, Male, 29 kg. (Fig. 13)

Time	B.P.	Pulse	Temp.	Observations
0				Usual preparation.
2:45	160	100	39	Immersion.
5:00	0		24	Ventricular fibrillation. Notice high temperature. Fibrillation at this phase may have been due to catheter in right ventricle. Dog could not be placed under proper perfusion before 10 minutes after fibrillation due to lack of ready connections.
5:15				Perfusion starts. Drip glucose plus Noradrenaline. B.P. not allowed below 50.
7:10	70	0	18.5	Very good color. Excellent fibrillation waves (Fig. 13, A).
7:45			17.5	Spontaneous defibrillation on further cooling (Fig. 13, B). Perfusion switched to brain perfusion and diameters of tubing in right side of heart equalized so that equal amount sent in each direction.
9:10			15	Perfusion has been interrupted completely for 1 hour but started again because of low blood pressure.
9:50			14	Rewarming starts. Min. blood flow, 200 c.c. Almost as soon rewarming is started, better heart action results (electrocardiogram and pulse rate).

Hypothermia combined with extracorporeal circulation
Oxygenator: Freshly donated lungs

Dog 110, Male, 21 kg. (Fig. 4)

Time	B.P.	Pulse	Temp.	Observations
0				Usual preparation.
4:20	140	140	37	Immersion (Fig. 4, A).
6:10	125		29	Dog has had 300 ml. 10 per cent glucose. Antihistaminics are given, intravenously. Blood pressure from 100 to 130, then dropped to 60, then came and stayed at 125.
7:25	80	35	22	Spontaneous respiration very superficial and minimal.
7:35			22	Perfusion from vein-to-vein started to help dog who has a very small pulse pressure. No appreciable results.
9:02	50	7	18.5	Perfusion toward brain and coronary started; obvious action on pulse rate (Fig. 4, E and F).
9:40	40	25	17	Pulse more regular. Good oxygenation of tissues.
9:47				Perfusion is stopped (Fig. 4, G).
9:56	25	5	16.5	Artificial respiration. 200 mg. Pentrozol toward brain in arterial catheter. Perfusion started again.
10:22		20	16.5	Attempts at producing ventricular fibrillation by means of electroshocks, unsuccessful.
11:45			15	Pulse is o.k.
12:12	60		14	Alternately right and left preponderance or bundle branch block. The drip of Noradrenaline is adjusted to keep B.P. at 60 mm. Hg. Min. blood flow = 80 per min.

13:47	80	60	20	One inhalation of 100 per cent CO_2 is given with immediate return of spontaneous respiration.
14:44	115		23.5	400 c.c. blood given (perfusion stopped). Dog has been hypoxic since beginning of rewarming. Moist râles heard over both lungs.
14:30	95		27	Blood pressure stable, coming slightly up.
14:55	128		29	Dog disconnected from machine. Tongue rather blue with turgid veins. Positive pressure breathing for 15 minutes with improvement, but it seems that despite correct heart action there is an inadequacy of blood to carry adequate oxygen.
15:05				Pentrozol 200 mg. and Psychoton 2 c.c. Soon after, dog shows signs of wakening. B.P. very unstable.
15:15			33	After transport from water to table, dog had suddenly an acute gross hemoptysis (bright red blood 250 c.c., followed by several others).

Autopsy: Lung hyperhemia and edema. Clots in filter.
Cause of death: Overdosed with fluids, possibly drug actions as well.

Extracorporeal circulation with deep hypothermia
Oxygenator: Donated lungs
Right ventricle cardiotomy

Dog 104, Male, 20 kg. (Fig. 5)

Time	B.P.	Pulse	Temp.	Observations
0				Usual preparation.
3:47	140		37	Immersion.
6:00	0	0	24	Ventricular fibrillation (Fig. 5, B). Perfusion starts with 4 minutes delay. Air embolism (2 big bubbles). Early fibrillation due to indwelling cardiac catheter. Min. blood flow, 200 c.c.
6:45				Spontaneous defibrillation (Fig. 5, D).
7:00			19	Troubles with pumps, some clots.
7:20			17	Ventricular fibrillation (Fig. 5, F). Cardiotomy, 33 minutes.
10:30			19	Chest closed.

After convenient rewarming it was possible to defibrillate the heart of this animal. But it did not beat well and steadily and fibrillated many times with shock defibrillation each time. At 38° C. nothing else was attempted, and the dog died.

At autopsy nothing worth mentioning was found.

Perfusion with disk oxygenator (improved technique) combined with hypothermia

Dog 124, Female, 24 kg.

Time	B.P.	Pulse	Temp.	Observations
0			38.5	Intraval intravenously, 1 Gm. Thereafter, ether.
1:45	110	110	38	Immersion in iced water.
6:25	80		19	Perfusion starts; directed downward into carotid artery. A cooling device surrounding machine helps in lowering rectal temperature. Calcium gluconate, 0.5 Gm./kg. (10 per cent).
6:45	35	16	17	Mydriasis right eye, myosis left. Blood going into dog 10° C.
8:00	40	3	12	Pulse recorded from oscilloscope.
8:30	32	0	10.5	Ca gluconate 10 per cent, 5 ml. Cardiac standstill. Then one beat is seen every 2 or 3 minutes.
9:20	30		9	One cardiac deflection seen every 4 to 5 minutes.
9:30	30		9.5	Rewarming starts. Cardiac standstill since 10 minutes. After warming device set into action, cardiac activity begins suddenly. Sudden pulse is 44.

10:30	70		19	Cedilanid, 1 ml. Shivering. Spontaneous respiration. Ectopic beats. Ca given again with improvement.
10:40	80		21	Perfusion stops.
11:00	100	60	24	Nystagmus and myosis.
12:20	130	140	30	Dog in good condition. Lot of shivering.
14:35	60		33	Has been taken out of bath. Seems to be shocked. B.P. dropping.
15:00	90		33	B.P. has come up slowly, good reflexes. Moves head.
16:00				Back in cage. Raises head; reacts on whistling.
26:00				Has left cage, drinks, one wound in neck is open; bleeds. Waves tail, very friendly. Hind legs very weak (barbiturate).
30				Found dead.

Autopsy report: Very large hemorrhage occurred from carotid artery. Very important hemorrhagic depot into left side of the neck subcutaneously. The importance of this hemorrhage is sufficient to believe it to have been responsible for this death.

THE EFFECT OF GANGLION BLOCKING AGENTS IN CONGESTIVE HEART FAILURE

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IN congestive heart failure, an increased venous pressure is an almost constant finding. This may be related to a reduction of cardiac output below the demand level and a rise in diastolic ventricular pressure which occur simultaneously in failure. With the left side of the heart at fault, an elevation of pulmonary capillary pressure and pulmonary artery pressure is manifested.[1,2] The increase in pressure observed in the systemic veins and in the vessels of the pulmonary circulation is the resultant of two factors: (a) An imbalance between the rate of ventricular filling and output with accumulation of the redistributed blood beyond the limits of normal distensibility of these vascular areas[3]; and (b) an elevated vasoconstrictor tone in the systemic veins[4] and pulmonary vessels.[2] This increased tonus may arise to some extent from the stimulus of relative local anoxia or other factors as yet undetermined.

The present work was initiated in an effort to evaluate the effect of ganglion blocking agents upon the elevated venous pressure in congestive heart failure. When it was satisfactorily demonstrated that a striking reduction in venous pressure occurred in these patients,[5] additional studies were made of vital capacity and peripheral blood flow before and after the exhibition of these drugs.

The agents employed were tetraethylammonium bromide (TEA) and hexamethonium iodide (HMI) which have been demonstrated to interfere with the transmission of sympathetic impulses by preventing the action of acetylcholine on ganglion cells and of parasympathetic impulses by interference at the effector cells. Thus, these agents will modify the effects of both sympathetic and parasympathetic stimulation.[6] The blockade imposed by these agents is the result of the similarity of their structures, as quarternary amines, to that of acetylcholine so that they can effectively compete to prevent transmission of impulses by blocking the receptor groups. Following the administration of tetraethylammonium bromide or hexamethonium bromide, there is produced (a) arteriolar and venous dilatation; (b) a decrease in peripheral resistance with drop in blood pressure in most instances; (c) tachycardia; (d) cutaneous vasodilatation; (e) a decrease in pulmonary pressure and pulmonary capillary resistance in pulmonary hypertension; (f) reduced bowel and bladder tonicity; (g)

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pupillary dilatation, accommodation loss, and partial ptosis of the lids.[6] The effect of these agents upon cardiac output in normal subjects and congestive failure patients has been variable.[2,6]

METHODS AND MATERIALS

Patients were selected from the medical service of Temple University Hospital. They had been admitted for the treatment of congestive heart failure. The etiologic diagnoses of the heart diseases were rheumatic disease with mitral stenosis, seven cases; hypertensive heart disease, nine cases; arteriosclerotic heart disease, four cases; and scoliotic heart disease, one case. Tetraethylammonium was given to four mitral stenosis patients, four hypertensive patients, and two arteriosclerotic patients; the remainder received hexamethonium. The patients were orthopneic; physical signs of pulmonary congestion, hepatomegaly, and peripheral edema were present in the majority. Many of these patients had been under treatment for cardiac failure for several years with digitalis and mercurial diuretics.

Venous pressures were obtained at the antecubital vein with the patient recumbent using an 18-gauge needle to which was attached a three-way stopcock accommodating a saline-filled manometer and a supply of saline to maintain a patent system.[5] The reference point was placed at 10 cm. from the back at the level of the right auricle. The vital capacity was determined by means of a Sanborn apparatus. The best maximal volume of air expired during three maximal inspirations was the accepted value. The vital capacity was measured only in the tetraethylammonium bromide-treated group.

Peripheral blood flow was measured using skin temperature determinations and finger or toe plethysmography in a constant temperature room. Digit blood flow determinations were carried out by the venous occlusion principle, employing the Burch-Winsor plethysmograph. By this method, the venous outflow from the digit is suddenly occluded by a miniature blood pressure cuff encircling the base of the digit without disturbing the arterial inflow. The change in volume of the distal phalanx then represents an indirect estimate of the arterial inflow. This is expressed quantitatively in cubic millimeters per second per 5 cubic centimeters. The details of the method are described by Robertson and associates.[7] We appreciate the limitations of this type of blood flow determination but believe that its accuracy is sufficient for the purposes of the present study. In some patients a finger was employed; in others, a toe.

In addition to the plethysmographic studies, skin-temperature changes were determined in fingers and toes. Copper constantan thermocouples were employed, fastened to the digits by strips of adhesive tape. The reference thermocouple was attached to the bulb of a thermometer in a Dewar flask. A Rubicon spotlight galvanometer was used. The determinations were carried out in a constant temperature room at 20°C. ± 1°. The subjects were studied in the fasting state. Care was taken to allow the digital skin temperatures to become stabilized before administering the blocking agent. This frequently required 45 to 60 minutes.

The blood pressure and pulse rate were observed frequently before and after the administration of the blocking agents. Neosynephrine was kept at hand to combat possible circulatory collapse. The patients were carefully observed for signs of pupillary dilatation or subjective effects such as dizziness, yawning, or other manifestations associated with the action of these drugs.

After satisfactory base-line records were obtained, the blocking agents were administered by slow injection into the adaptor of the intravenous drip attached to the venous pressure needle. The dose of tetraethylammonium bromide varied from 150 to 500 mg. depending upon the size of the patient and severity and type of cardiac disease. The dose of hexamethonium bromide employed varied from 12.5 to 50 mg. based upon the same considerations, being about one-tenth that of tetraethylammonium bromide. The effects of the administration were recorded until the maximal changes had been observed and a definite return of the blood pressure toward the base-line levels was noted. Following the termination of the study, the patient was returned to his bed and was kept flat for two hours with frequent blood pressure readings being obtained.

A small group of patients was studied in whom congestive failure was not present in order to observe the effect of these agents on venous pressure and circulatory dynamics in the absence of heart failure. These patients had been hospitalized for treatment of various conditions including diabetes mellitus, myositis, rheumatoid arthritis, lymphedema praecox, and hypertension.

RESULTS

The most impressive effect of the autonomic blockade imposed by these agents was that of relief of dyspnea and orthopnea. This factor is largely subjective rather than objective and for that reason cannot be readily measured. It was noted that patients who could not rest comfortably in recumbency prior to the test could do so without distress during and after the period of observation. Several patients volunteered that they could breathe more easily than had been possible for many months previously. However, these benefits were of short duration in most instances, lasting only for 24 to 48 hours. It is difficult to reason that the improvement noted was due to psychological factors, although the preparations for the procedure could not have failed to impress the patient.

TABLE I. CHANGES IN VENOUS PRESSURE AND VITAL CAPACITY FOLLOWING ADMINISTRATION OF GANGLION BLOCKING AGENTS

		BEFORE	AFTER
A. Venous pressure (mm. saline)			
Heart failure (average of 21 cases)		174.5	85.0
Controls (average of 7 cases)		113.4	76.4
B. Vital capacity (c.c. air)			
Heart failure (10 cases)	Range	920-1890	1221-2416
	Average	1620	2122

The effect on venous pressure in the patients with congestive failure was pronounced. In each instance, the venous pressure dropped precipitously, simultaneously with the drop observed in arterial pressure. However, in certain patients, the drop in venous pressure was significantly greater than the change in arterial pressure. During the period of recovery from the hypotensive effect of the blocking agent, it was noted that the venous pressure began to rise con-

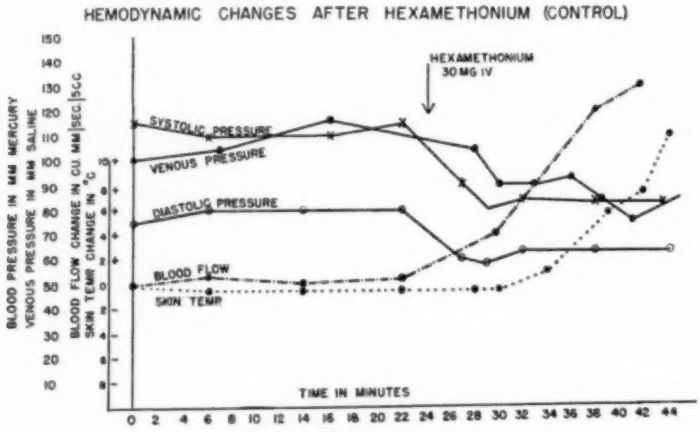

Fig. 1.

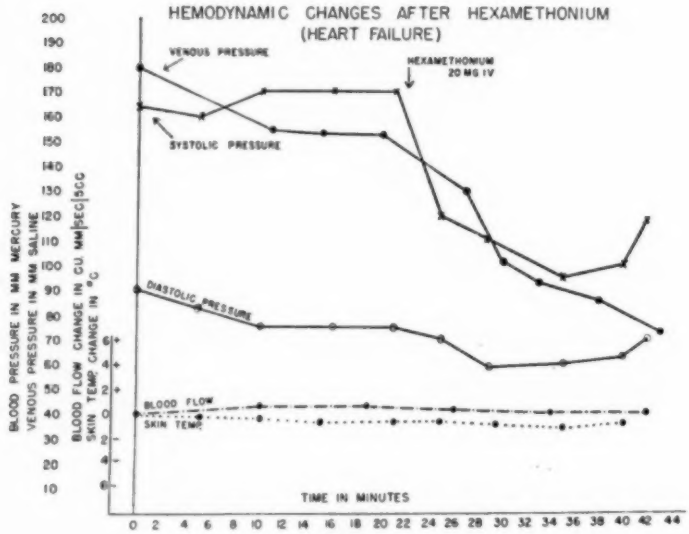

Fig. 2.

currently with the arterial pressure. However, the venous pressure did not rise to the abnormal levels observed during the preinjection period. These determinations were not repeated after the total effect of the injection had been dissipated. The reductions in arterial and venous pressures observed in the heart-failure patients also occurred in the control group after hexamethonium with two exceptions. In these two patients, the failure of the pressures to decrease may have been due to somewhat inadequate dosage, although there were increases in skin temperature.

The corresponding drops seen in venous pressure and arterial pressure in most instances and the failure of these indices to change in two patients suggest that the vasodilator effect produced by these agents occurs as the result of the inhibition of venous and arterial constrictor impulses simultaneously. However, the possibility that arteriolar dilatation reduces the rate of flow into the venous side to such an extent that venous pressure falls because of a reduction of venous blood volume has not been excluded.

TABLE II. HEMODYNAMIC CHANGES FOLLOWING ADMINISTRATION OF CERTAIN BLOCKING AGENTS TO ELEVEN PATIENTS WITH CONGESTIVE HEART FAILURE AND SEVEN CONTROL SUBJECTS

	DIGITAL PLETHYSMOGRAPH CHANGES	SKIN TEMP. CHANGES	ARTERIAL PRESSURE	VENOUS PRESSURE	PULSE	DIAGNOSES
A. *Patients with heart failure*						
1.	−	−	−	−	−	H.C.V.D.
2.	°	°	−	−	+	H.C.V.D.
3.		−	−	−	−	A.S.H.D.
4.		°	−	−	°	H.C.V.D.
5.		−	−	−	°	M.S.
6.	+	+	−	−	−	H.C.V.D.
7.	°	°	−	−	−	A.S.H.D.
8.	°	°	−	−	+	S.H.D.
9.	°	°	−	−	°	M.S.
10.	°	−	−	−	−	H.C.V.D.
11.	+	(finger) ° (toes) +	−	−	−	M.S.
B. *Control subjects*						
1.	++	++	−	−	+	Neurosis
2.	−	+	−	−	+	Diabetes
3.	++	++	°	°	°	Hypertension
4.*	°	−	−	−	+	Hypertension
5.		+	−	−	++	Dermatitis
6.		+	−	−	++	Arthritis
7.		(finger) + (toes) °	−	−	+	Lymphedema Praecox

++ Marked increase
\+ Increase
° No change
− Decrease
* Peripheral circulatory collapse

H.C.V.D. Hypertensive heart disease
A.S.H.D. Arteriosclerotic heart disease
M.S. Mitral stenosis
S.H.D. Scoliotic heart disease

Digital skin temperature changes and measurement of blood flow by the digital plethysmograph showed highly variable results. These methods give no information concerning changes in blood flow in muscle or visceral areas where significant effects are known to occur. In several patients, significant drop in venous pressure and arterial pressure was unaccompanied by changes in skin temperature. It may be assumed here that the principal action of the drug was on visceral or muscle blood flow with dilatation occurring in these areas to reduce peripheral resistance. In one noncardiac patient, a severe syncopal reaction occurred in which a marked drop in skin temperature was observed. In this instance it may also be assumed that pooling of blood occurred in the visceral or muscle vascular beds.

In five of the eleven heart failure patients, no change in skin temperature or plethysmographic readings was observed. In four other failure patients, a drop in skin temperature was observed; in two, there was a rise in skin temperature associated with an increase in blood flow by plethysmograph. In contrast, the skin temperature rose in six of the seven nonfailure patients and fell in the one patient of this group who experienced circulatory collapse. Thus, the usual increase in cutaneous flow described as an effect of the blocking agents is largely absent in the patients with congestive heart failure. This suggests that neurogenic constrictor impulses in other areas such as in the viscera or muscles may be the principal site of blockade in patients with congestive failure.

DISCUSSION

Our observations initially reported in 1950[5] indicated that the administration of ganglion blocking agents in patients with congestive failure was capable of reducing the venous pressure simultaneously with the arterial pressure, of increasing the vital capacity, and of ameliorating dyspnea and orthopnea. A similar study had appeared previously with comparable results in a group of patients with hypertensive heart disease.[8] Subsequently, a report in 1951 by Smirk and Alstad[9] described marked improvement in several patients with congestive failure following autonomic blockade. They noted a reduction in dyspnea and pulmonary congestion, an increase in vital capacity from 0.9 liters to 2.1 liters in one patient, a reduction in heart size, improvement in exercise tolerance and in the electrocardiogram following pentamethonium. More recently, Kelley and associates[10] reported favorably on the use of hexamethonium in eighteen patients with various types of cardiac disease in decompensation. With long-term administration of hexamethonium they state that it has been possible occasionally to discontinue digitalis and diuretic therapy. However, one patient reported by Turner[11] obtained no benefit from treatment with pentamethonium over a three-day period.

In the observations reported here, twenty-one patients with various types of heart disease including hypertension, arteriosclerosis, and valvular heart disease with congestive failure have received either tetraethylammonium bromide or hexamethonium iodide. In each instance, there has been subjective improvement associated with an increase in vital capacity and a drop in venous pressure.

The studies conducted on peripheral blood flow indicate that in the congestive-failure patients the usual increase in flow observed in the extremities, as manifested by cutaneous vasodilatation and increase in digital plethysmographic readings, is lacking. Nonfailure patients studied under the same conditions manifested an increase in skin temperature and digital flow. However, both groups showed a comparable drop in venous pressure and arterial pressure. The observations of Freis and associates[12] on blood flow in different vascular areas following hexamethonium indicate that vasoconstrictor impulses are of greater importance in the hands and feet and of less importance in muscles and viscera. They observed marked increases in digit flow with some decrease in flow to muscles, liver, and kidney areas. The finding of increased digital flow in the noncardiac group corresponds to the observations of Freis and associates.[12]

The absence of similar changes in the heart-failure patients with comparable reductions of venous and arterial pressures indicated other vascular areas have been affected in the latter group. If increased vasoconstrictor impulses are present in the visceral circulation in heart failure, the action of the blocking agents may be manifested principally in these areas where the greatest tonicity exists. The dosage of the blocking agent employed was capable of releasing certain areas from vasoconstrictive impulses but not of producing cutaneous vasodilatation as in the control group. However, the studies of Myers and Hickam[13] on hepatic blood flow in congestive failure indicate there is no increase in resistance in the hepatic capillary bed since the rate of flow was closely correlated with cardiac output.

The beneficial effect of autonomic blockade in congestive failure may be the result of the pooling of blood beyond the central cardiopulmonary area.[2,14] The present study does not determine the sites into which the redistribution of blood volume is accomplished. However, since recent evidence reported by Ross and associates[15] suggests that there may be little or no alteration in blood volume in congestive failure, the elevated venous pressure may represent blood displaced from the small vessels, and possibly the arterial circulation, into the large veins. The release of these areas from vasoconstrictive impulses by tetraethylammonium bromide and hexamethonium iodide permits a reduction of venous pressure and shifting of the blood volume with resulting clinical improvement. Halmagyi and associates[4] have accumulated evidence to show that venous hypertension in heart failure is mediated by neurovascular reflexes leading to venous constriction. The blocking of neurogenic impulses decreases venoconstriction and reduces venous pressure. The fall in venous pressure may lower the intracavitary pressures within the heart so that more effective myocardial contraction can be achieved.[3] In addition, hexamethonium bromide has been shown to reduce pulmonary capillary and pulmonary artery pressures.[1,2,14] With lessened venous return and peripheral pooling of blood, Werko and associates[14] have shown a decrease of approximately one-third in the cardiopulmonary blood volume following administration of hexamethonium. This would account of the relief of symptoms of dyspnea and orthopnea and for the increase in vital capacity observed in the present work.

SUMMARY

Autonomic blocking agents, tetraethylammonium bromide and hexamethonium iodide, were demonstrated to lower the venous pressure simultaneously with arterial pressure and to increase vital capacity in patients with congestive heart failure. Following the administration of these agents, significant clinical improvement was observed with a reduction in the degree of dyspnea and orthopnea. The duration of the improved status as evaluated clinically varied from one to several days, those with milder degrees of congestive failure experiencing longer benefits. Measurements of skin temperature and digital blood flow revealed that the usual increase noted in nonfailure patients was absent in most patients with congestive failure. The reduction of venous and arterial pressures without evidence of increased cutaneous or digital flow suggests that a redistribu-

tion of blood volume has occurred by the release of vasoconstrictor reflexes probably in splanchnic or muscular areas. The release of neurogenic reflexes increasing the arteriolar and venular tone will reduce the work load of the left ventricle and decrease the elevated venous filling pressures of the right heart. The use of autonomic blockade as a method of treatment for pulmonary congestion has been shown to be effective.

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THE CARDIOVASCULAR AND RENAL HEMODYNAMIC EFFECTS* OF ARAMINE

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IN recent years there has been much interest centered on the effectiveness of various pressor agents in the treatment of hypotensive states from various causes. One of the more recent of these agents to be investigated is a synthetic sympathomimetic amine which has been called Aramine (Levo-1-(m-hydroxyphenyl)-2-amino-1-propanol).† Chemically this agent falls into the group of m-hydroxyphenylalkylamines along with neosynephrine, which has been found to have greater pressor activity than most of the other synthetic agents. Aramine has the advantage of combining this high order of pressor effectiveness along with a certain refractoriness to elimination which prolongs its duration of action.[1] This is contrasted to the more evanescent action of norepinephrine. Studies on Aramine in the experimental animal have failed to show a tachyphylactic response to repeated injections and no primary or secondary fall in blood pressure has been noted. This drug apparently also shares with neosynephrine the freedom from toxic effects on the heart and the development of abnormal rhythms so often seen with the administration of some of the more active catechol derivatives.[2]

Clinical reports indicate that norepinephrine is effective in the treatment of normal volemic shock but rather marked renal vasoconstriction has been observed[3,4] when this agent was infused into normal individuals. Since Aramine has similar peripheral arteriolar action it has been thought advisable to study its effect on the renal vasculature as well as on cardiac hemodynamics of normal subjects in order to furnish a comparison with the effects of norepinephrine on these vascular beds.

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*The effects on water and electrolyte excretion were also studied.

†Furnished by Sharp and Dohme, Inc.

METHODS

Renal Studies.—In studying the effects on renal hemodynamics the drug was given to nine normal subjects. In all cases 15 mg. of Aramine were added to 500 c.c. of 5 per cent glucose in distilled water and administered as an intravenous infusion at a rate fast enough to induce an increase in the mean blood pressure of 30 mm. Hg or more. The pressor response began between 3 and 15 minutes after the infusion was started.

Inulin was used to estimate the glomerular filtration rate (GFR) and para-aminohippurate (PAH) was used to estimate renal plasma flow (RPF). The methods and techniques have previously been described.[5] Sodium and potassium determinations were done on all blood and urine samples using the Beckman analytical technique. In all cases 3 ten-minute collection periods (control studies) were carried out prior to the administration of the drug. After satisfactory blood pressure levels had been achieved with the drug, 4 to 6 ten-minute collection periods were obtained while the infusion was continued and the blood pressure remained elevated. Observations on the blood pressure and pulse rate were made by auscultation at one-minute intervals after the drug was started. Electrocardiographic tracings were made before and after the height of the blood pressure response and after the administration of atropine sulfate in doses of 0.65 mg. given intravenously.

Cardiovascular Studies.—The cardiovascular effects were studied in seven normal subjects utilizing the method of catheterization of the right side of the heart. The Fick principle was used for the determination of cardiac output. The same dosage levels of Aramine were employed as in the renal studies noted above. Oxygen content in the blood samples was routinely determined by the Roughton-Sholander microanalytical technique. The samples on two patients were also analyzed by the Van Slyke manometric technique as a check on the usual analytical method used. Favorable comparisons were found in both cases. Oxygen consumption was determined by using the Collins respirometer. Intracardiac and pulmonary arterial pressures were recorded before and at frequent intervals during the pressor response to the Aramine using the Sanborn electromanometer. Auscultatory blood pressure and pulse records were kept at one minute intervals during the drug administration and electromanometric recordings from the radial artery were made at ten-minute intervals. Cardiac output was determined before the drug and at the height of the blood-pressure response, and again after the administration of 0.65 mg. of atropine sulfate intravenously in four of the patients. Electrocardiographic tracings were again recorded at the time of the cardiac output determinations.

The following formulas were used for calculating total peripheral resistances and left ventricular work:[6]

$$\text{TPR} = \frac{\text{BA}_m - 0}{\text{CO}} \times 1{,}332 \text{ dynes/sec./cm.}^{-5} \qquad (1)$$

$$\text{LVW} = \frac{\text{CI} \times 1.055 \times (\text{BA}_{m\text{-}5}) \times 13.6}{1000} \text{ kg. M./minute/sq. M.} \qquad (2)$$

Where

BA_m—Mean brachial arterial pressure in mm. Hg
CO—Cardiac output in c.c./sec.
1,332—Conversion factor from mm. Hg to dynes/cm.$^{-5}$
CI—Cardiac index, liters/minute/sq. meter of body surface
1.055—Specific gravity of blood
13.6—Specific gravity of mercury
5—Assumed left ventricular diastolic pressure mm. Hg

RESULTS

Renal Studies.—There was no consistent effect on respiration in these patients. However, several individuals in the group showed manifestations of anxiety (including an increased respiratory rate) as the blood pressure was elevated. Several of them complained of a sense of constriction in the chest without pain. Four of the patients developed moderately severe occipital headaches. Most of the patients showed a pilomotor response. The pulse rate decreased significantly in all but one patient. If atropine was then given the pulse rate increased above the control levels.

The renal hemodynamic effects of Aramine infusion on the nine normal subjects are presented in Table IA. The glomerular filtration rate was not altered significantly despite an increase in the mean blood pressure from 86 mm. Hg to 125 mm. Hg in the second postdrug period (D_2). There was a slight reduction in the average renal blood flow (RBF) from 1,134 ml./min. to 1,038 ml./min. (94 per cent of control), whereas renal vascular resistance increased to 162 per cent (average) of the control value. Despite the renal vasoconstriction due to Aramine, the increase in renal vascular resistance and the reduction in renal blood flow were not as great as after the administration of norepinephrine (Table IA) although the increment of blood pressure elevation after both drugs was about the same (Table IA).[7] However, a larger group of patients should probably be observed if conclusive deductions are to be made in this respect. Glomerular filtration rate as estimated by creatinine clearance did not appear to be altered significantly except for two patients on whom 6 periods were completed. This is similar to previous studies with norepinephrine.[7] After Aramine there was only a slight increase in the filtration fraction from 0.16 to 0.18 (D_2).

Apparently blood pressure elevation with Aramine had no consistent effect on the urine volume. Although this tended to increase during the studies, the change was not statistically significant ($p > 0.5$) during periods D_1 and D_2. However, during period D_3 the change was just barely significant ($p < 0.10$). At least there was no evidence of an antidiuretic response. The average sodium excretion increased from 0.197 meq./min. to 0.222 meq./min. during the second drug infusion period (D_2) (120 per cent of control) and to 0.310 meq./min. (165 per cent of control) in the third period (D_3). This increase in sodium excretion may have been related in some instances to fluctuations in water diuresis during the study rather than due to alterations in hemodynamics since the excretion rate of sodium was quite erratic. It was probably not due to alterations of sodium concentration in the plasma, since the concentration of this electrolyte was not altered appreciably. These increases in sodium excretion were not statistically significant except during periods D_3 ($p < 0.30$) and D_4 ($p < 0.10$). Potassium excretion was not altered significantly.

TABLE IA. RENAL HEMODYNAMIC AND BLOOD PRESSURE RESPONSE TO CONTINUOUS INTRAVENOUS INFUSION OF ARAMINE

PATIENT	GLOMERULAR FILTRATION RATE‡					RENAL BLOOD FLOW*					MEAN BLOOD PRESSURE**					RENAL VASCULAR RESISTANCE***				
	C	D_1	D_2	D_3	D_4	C	D_1	D_2	D_3	D_4	C	D_1	D_2	D_3	D_4	C	D_1	D_2	D_3	D_4
1. W.A.	107	127	126	138	138	1402	1514	1263	1076	1439	95	107	129	135	120	.067	.070	.102	.125	.083
2. S.K.	80	80	83	73	92	1049	1195	995	962	1038	112	116	122	127	142	.106	.097	.122	.132	.137
3. E.P.	79	81	88	84	70	736	782	721	766	797	86	123	146	127	124	.116	.157	.202	.166	.155
4. G.J.	94	111	94	97	103	1059	991	916	984	1114	90	122	131	125	139	.084	.123	.143	.127	.125
5. M.T.	118	124	131	—	—	1795	1549	1307	—	—	78	122	128	131	—	.043	.078	.097	—	—
6. E.F.	75	64	81	76	—	972	891	904	1075	—	77	105	122	122	—	.079	.117	.135	.113	—
7. C.T.	150	146	130	140	—	1330	1166	1085	847	—	75	121	116	117	—	.056	.104	.107	.138	—
8. S.S.	124	110	174	139	—	1105	1007	1411	1451	—	80	116	120	105	—	.072	.115	.085	.072	—
9. J.A.	67	61	70	70	—	755	680	741	698	—	84	115	115	118	—	.111	.109	.155	.169	—
Mean	99	100	109	102	101	1134	1086	1038	982	1097	86	116	125	123	131	.082	.108	.128	.130	.125
Mean of per cent of control†		101	109	105	111		97	94	96	104		137	147	144	138		139	162	156	134
Norepinephrine (Mean)§	108		102			1143		705			97		132			.091		.195		
Mean of per cent of control for norepinephrine†		—	94			—		63			—		136			—		224		

C—Control (average of 3-10 minute periods)
D_1—First 10-minute collection period during Aramine infusion
D_2—Second 10-minute collection period during Aramine infusion
D_3—Average of third and fourth 10-minute collection periods during Aramine infusion
D_4—Average of fifth and sixth 10-minute collection periods during Aramine infusion

*—Renal blood flow in ml./minute = $\frac{\text{Renal plasma flow}}{\text{1–Hematocrit}}$

‡—Glomerular filtration rate ml./minute (Inulin clearance)

**—Mean Blood Pressure = Diastolic plus 1/3 of pulse pressure

***—Renal Vascular Resistance = $\frac{\text{Mean blood pressure}}{\text{Renal blood flow}}$

†—Mean of per cent of control = Mean value for $\frac{\text{Drug observation}}{\text{Control observation}} \times 100$

§—Mean for nine patients.

TABLE IB. THE EFFECT OF CONTINUOUS INTRAVENOUS INFUSION OF ARAMINE ON CREATININE CLEARANCE, RENAL PLASMA FLOW, AND HEMATOCRIT*

PATIENT	AGE	DOSE ARAMINE†				CREATININE CLEARANCE‡					RENAL PLASMA FLOW‡					FILTRATION FRACTION§					HEMATOCRIT		
		D_1	D_2	D_3	D_4	C	D_1	D_2	D_3	D_4	C	D_1	D_2	D_3	D_4	C	D_1	D_2	D_3	D_4	C	D_2	D_4
1. W.A.	51	.24	.10	.00	.00	128	137	137	136	138	869	954	796	667	892	.12	.13	.16	.21	.15	38	37	38
2. S.K.	62	.12	.12	.10	.15	63	59	63	66	63	661	705	587	577	623	.12	.11	.14	.13	.15	37	41	40
3. E.P.	41	.18	.05	.12	.12	75	88	77	81	94	449	446	411	444	462	.18	.18	.21	.19	.15	39	43	42
4. G.J.	39	.05	.05	.05	.05	86	106	90	99	127	572	545	504	502	568	.16	.20	.19	.19	.18	46	45	49
5. M.T.	27	.10	.06	.09	—	102	109	98	—	—	987	883	745	—	—	.12	.14	.18	—	—	45	43	45
6. E.F.	41	.12	.24	.12	—	98	101	95	123	—	515	472	479	570	—	.15	.14	.17	.13	—	47	47	47
7. C.T.	28	.15	.15	.00	—	121	98	112	94	—	798	688	640	491	—	.19	.21	.20	.29	—	40	41	42
8. S.S.	32	.12	.11	.16	.06	—	—	—	—	—	652	554	776	711	—	.19	.20	.22	.20	—	41	45	51
9. J.A.	28	.05	.15	.12	.12	78	54	75	75	—	370	333	363	363	—	.18	.18	.19	.19	—	51	51	48
Mean		.13	.11	.11	.10	94	94	93	96	106	653	620	589	541	636	.16	.17	.18	.19	.16	43	44	45
Mean of per cent of control							100	100	105	120		95	92	91	100		106	120	120	112		103	105
Norepinephrine (Mean values—9 patients)						120	—	118	—	—	706	—	417	—	—	.17	—	.28	—	—			
Mean of per cent of control for norepinephrine								98					60					167					

*See Table IA for key to abbreviations (C and D_1 to D_4)

‡—ml./minute

§—Filtration fraction, $\frac{\text{Glomerular filtration rate (inulin, Table IA)}}{\text{Renal plasma flow}}$

†—Infusion rate per minute in milligrams.

TABLE II. EFFECT OF CONTINUOUS INFUSION OF ARAMINE ON THE URINARY EXCRETION OF WATER AND ELECTROLYTES

PATIENT	URINE VOLUME (ML./MIN.)					PLASMA SODIUM (MEQ./L.)					PLASMA POTASSIUM (MEQ./L.)					SODIUM EXCRETION (MEQ./MIN.)					POTASSIUM EXCRETION (MEQ./MIN.)				
	C	D_1	D_2	D_3	D_4	C	D_1	D_2	D_3	D_4	C	D_1	D_2	D_3	D_4	C	D_1	D_2	D_3	D_4	C	D_1	D_2	D_3	D_4
1. W.A.	12.8	14.2	14.8	20.2	24.8	143	138	140	143	141	5.0	5.6	4.8	4.7	4.9	.420	.451	.360	.560	.710	.051	.059	.059	.060	.073
2. S.K.	7.9	9.3	10.1	12.2	14.0	146	144	147	149	147	4.8	4.9	4.7	5.3	4.5	.141	.156	.145	.130	.182	.051	.067	.063	.057	.058
3. E.P.	4.8	1.5	1.9	3.8	4.8	149	146	144	147	147	2.9	2.9	2.9	2.6	2.9	.321	.354	.346	.528	.750	.069	.083	.081	.089	.101
4. G.J.	9.0	10.0	10.8	13.0	27.0	153	155	146	150	152	5.7	5.8	5.1	5.2	5.0	.076	.077	.037	.160	.188	.054	.059	.056	.069	.075
5. M.T.	6.8	6.0	5.0	5.6	—	139	141	146	142	—	4.3	4.6	3.9	4.2	—	.241	.241	.243	.161	—	.046	.036	.036	.020	—
6. E.F.	6.2	9.9	14.5	14.3	—	144	150	147	147	—	4.5	4.5	4.3	4.4	—	.318	.310	.431	.690	—	.078	.089	.106	.125	—
7. C.T.	14.7	17.2	14.5	14.5	—	140	138	139	139	—	3.8	3.5	3.7	3.8	—	.069	.064	.054	.046	—	.034	.024	.019	.016	—
8. S.S.	5.3	3.8	9.7	11.6	—	133	131	—	137	—	5.3	4.8	—	5.3	—	.075	.056	.096	.147	—	.039	.035	.047	.037	—
9. J.A.	8.8	12.3	—	16.0	—	140	140	143	141	—	3.4	3.0	2.8	3.0	—	.110	.075	.230	.370	—	.015	.011	.009	.010	—
Mean	8.5	9.4	10.2	12.4	17.7	143	143	144	144	147	4.4	4.4	4.0	4.3	4.3	.197	.198	.222	.310	.458	.049	.051	.053	.054	.077
Mean of per cent of control		105	124	150	193		100	100	101	100		99	94	97	95		96	120	165	195		100	101	100	136

C—Control (average of 3 collection periods)

D_1 to D_4—Successive periods after blood pressure elevation with continuous infusion of Aramine (see footnotes Table I A).

Cardiovascular Studies.—The cardiodynamic effects of Aramine administration are presented in Tables III A and III B. It is noted that with an increase in both the systolic and diastolic blood pressures there is associated a marked slowing of the pulse rate. The control values recorded are the averages in each case of all readings during this period. All values tabulated after the drug was started under the various measurements listed are the results obtained at the time cardiac output determinations were made. The cardiac index was found to be essentially unchanged, the average being 3.85 L./min./sq. M. of body surface before and 3.75 L./min./sq. M. of body surface during the Aramine infusion. After the administration of atropine there was a striking increase in cardiac output in three of the four patients studied. This was associated with a sharp increase in the pulse rate to values greater than the control observations. In one case (M.Jq.) no change in the pulse rate occurred during the Aramine infusion but it increased from 80/min. to 120/min. after atropine, and the cardiac index increased about two and one-half times over the control level. The pulse rate did not increase above the control levels in the only patient who did not show an increase in cardiac output after atropine.

Pulmonary artery pressure increased from an average control level of 17 mm. Hg to 30 mm. Hg with the Aramine infusion. The administration of atropine produced no further change. The arteriovenous oxygen difference increased from 4.5 volume per cent to 5.0 volume per cent with the drug but was again found at the control levels after atropine. Total oxygen consumption increased from 294 ml./min. to 321 ml./min. with a slight further increase to 36) ml./min. after atropine.

The total peripheral resistance was elevated from 1,136 dynes /sec./cm.$^{-5}$ to 1,715 dynes /sec./cm.$^{-5}$ along with the increase in blood pressure. However, after the administration of atropine and the associated increase in the cardiac output the total peripheral resistance usually decreased. Left ventricular work correlates with the degree of pressor response and changes in the cardiac index showing a progressive increase from control levels of 4.76 kg. M./min./M.^{2} (which is normal) to 6.78 during the Aramine infusion and to 10.4 after the atropine.

Electrocardiographic tracings revealed a sinus bradycardia in nearly all cases. This returned to the control rate or greater after atropine. One case (E. F., Group 1) showed a slight transient S-T segment depression in precordial Leads V_2 to V_4 and an inverted T wave in V_2 which was not altered by atropine.

Several of the patients in Group 2 (cardiac output studies) showed an increase in respiratory rate but this was inconstant. Occipital headaches were observed in five patients as the blood pressure increased. This was excruciating in one of the patients and was associated with a tight feeling across the chest, anxiety, slurred speech, and visual disturbances. The side reactions were thought to be due to the acute elevation in blood pressure to hypertensive levels rather than due to a direct effect of the drug per se.

TABLE IIIA. EFFECT OF ARAMINE ON BLOOD PRESSURE, PULSE RATE, AND CARDIAC OUTPUT

PATIENT	BLOOD PRESSURE						PULSE RATE			CARDIAC OUTPUT			CARDIAC INDEX		
	SYSTOLIC			DIASTOLIC											
	C	ARA	AT	C	ARA	AT	C	ARA	AT	C	ARA	AT	C	ARA	AT
M.J.	120	194	196	70	90	108	80	58	100	9.4	7.2	11.6	5.24	4.20	6.50
J.H.	130	186	186	70	100	100	84	58	126	5.2	5.0	6.2	2.75	2.64	3.28
M.Jq.	110	208	218	70	100	108	80	80	120	5.4	6.6	13.8	3.48	4.30	8.90
J.G.	118	206	—	70	100	—	88	78	—	7.0	7.2	—	4.00	4.15	—
A.R.	140	210	—	90	120	—	78	62	—	6.2	5.7	—	3.60	3.28	—
W.P.	130	200	180	80	116	120	88	50	90	5.7	6.6	5.0	3.30	3.82	2.90
J.B.	132	182	—	70	110	—	86	58	—	8.3	7.0	—	4.60	3.86	—
Average	126	198	195	74	105	109	83	63	109	6.7	6.5	9.2	3.85	3.75	5.40
Mean of per cent of control		157	161		142	150		76	132		99	147		104	147

Systolic—Systolic blood pressure in mm. Hg
Diastolic—Diastolic blood pressure in mm. Hg
Cardiac Output—Liters/minute
Cardiac Index—Cardiac output per square meter of body surface
C—Control
Ara—During Aramine Infusion
At—After atropine but Aramine infusion continued

TABLE IIIB. EFFECT OF BLOOD PRESSURE ELEVATION WITH ARAMINE ON PULMONARY ARTERY PRESSURE, PERIPHERAL RESISTANCE, LEFT VENTRICULAR WORK, AND OXYGEN CONSUMPTION*

PATIENT	A-V O_2† DIFFERENCE			TOTAL O_2‡ CONSUMPTION			PA PRESSURE			TPR			LV WORK§		
	C	ARA	AT	C	ARA	AT	C	ARA	AT	C	ARA	AT	C	ARA	AT
M.J.	3.8	5.2	4.3	358	378	500	18	38	23	740	1388	945	6.17	7.24	12.30
J.H.	5.4	6.4	5.4	280	322	335	18	38	38	1382	2060	1665	3.35	4.70	5.84
M.Jq.	3.9	3.5	2.3	211	230	318	15	25	28	1230	1650	840	3.90	8.08	17.84
J.G.	4.1	4.1	—	286	296	—	18	35	—	990	1500	—	4.65	7.75	—
A.R.	5.1	5.6	—	318	318	—	25	30	—	1372	2120	—	5.26	6.82	—
W.P.	5.2	4.2	5.7	296	276	286	14	21	25	1361	1745	1870	4.36	5.75	5.63
J.B.	3.7	6.1	—	308	425	—	8	25	—	874	1540	—	5.66	7.15	—
Average	4.5	5.0	4.4	294	321	360	17	30	29	1136	1715	1330	4.76	6.78	10.40
Mean of per cent of control		115	96		109	127		195	176		155	113		146	240

*See Table III A for key to abbreviations
†—Arterial (radial) blood oxygen concentration in volume per cent minus mixed venous blood (pulmonary artery) oxygen concentration
‡—Oxygen uptake by the lungs in ml./minute
§See text for description
PA Pressure—Pulmonary artery pressure in mm. Hg
TPR—Total peripheral resistance§

DISCUSSION

Investigation in recent years has shown that decreased peripheral vascular tone is an important sustaining factor in certain hypotensive states. Norepinephrine and some of the synthetic vasopressor drugs have been found to correct this abnormality in vascular tonicity by inducing a state of generalized peripheral vasoconstriction.[3] One disadvantage of this form of therapy has been the increase in cardiac irritability and associated development of arrhythmias especially in the presence of myocardial ischemia and anoxia.[2,8] Another has been the evidence of renal vasoconstriction and marked reduction in renal blood flow when norepinephrine is infused. Skelton and his associates[4] have reported on the renal hemodynamic effects with norepinephrine in normal individuals and the results

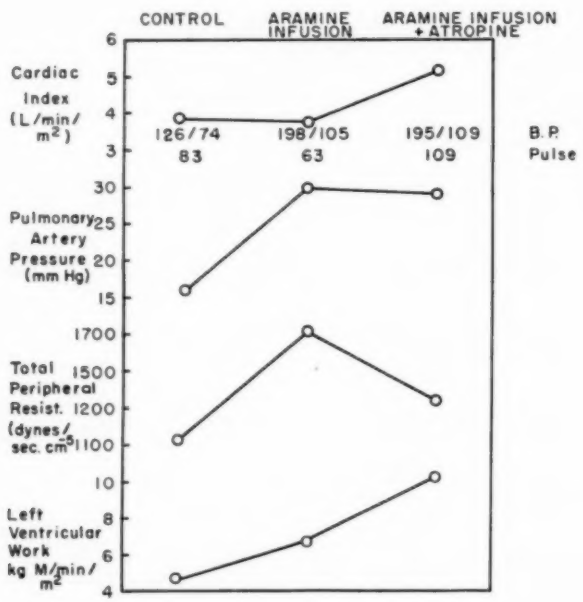

Fig. 1.—Hemodynamic effects of Aramine infusion. Average results in seven normal subjects. The mean values for changes in cardiovascular hemodynamics are plotted for the various functions after Aramine, and then after Aramine plus atropine.

of this work are compared with Aramine in Tables IA and IB. It is seen that with greater degrees of pressor response during Aramine administration as compared to norepinephrine, there is less reduction in the renal blood flow and consequently less evidence of renal vasoconstriction. Renal vasoconstriction would seem to be potentially an undesirable effect when it occurs to any degree during the use of these drugs as therapeutic agents. The observations of a less intense reduction in the renal blood flow during Aramine infusion as compared to norepinephrine would appear to be an advantage of the former drug. However, it should be emphasized that the observations herewith presented cannot be directly transferred to the response when either drug is used for the treatment

of shock. Under the latter circumstances entirely different hemodynamic responses may be elicited. As yet there is no information available on the effect of either of these drugs on the renal circulation or on cardiac output in cases treated for shock due to hemorrhage and other causes. Moyer and Mills[5,7] have demonstrated, however, that the markedly reduced glomerular filtration rate during acute hexamethonium-induced hypotension rises toward normal when norepinephrine is given. This is suggestive evidence that the renal hemodynamics during the administration of vasopressor agents will be different in patients with shock and other hypotensive states as compared to normal subjects with normal blood pressures.

The total effect of Aramine as with norepinephrine is one of general vasoconstriction with little or no change in cardiac output as seen in Fig. 1. Similarly also there is an increase in both the systolic and diastolic blood pressures associated with a reduction in pulse rate. The latter is probably due to a reflex action on the pacemaker being mediated via the vagus nerve since it can be promptly abolished by atropine. This has also been found true with other synthetic pressor amines, notably methoxamine.[9] The increase in pulmonary artery pressure is also a characteristic finding with most of the pressor drugs.

The change in cardiac output after atropine is probably related simply to the increase in pulse rate which occurred. Conversely, when a reduction in cardiac output was noted initially a bradycardia was also observed. Since total peripheral resistance, here represented, is merely a mathematical calculation, it varies with the cardiac output and the blood pressure rather than because of any specific functional alteration per se.

A question may be raised as to the practical applicability in certain circumstances of a drug which increases left ventricular work so greatly. One must be reminded again that a different set of circumstances existed here when the blood pressure was increased from normotensive levels to hypertensive levels than would ordinarily exist in the clinical use of Aramine when the blood pressure would be raised from hypotensive levels to normotensive ones. Until such a time arises when the hemodynamics are actually measured under hypotensive conditions and during the response to therapy with these pressor agents, the true pharmacodynamics in these situations must remain a matter of conjecture.

The electrocardiographic studies during the drug administration indicated no evidence of increase in cardiac irritability.

CONCLUSIONS

Aramine is a potent synthetic vasopressor agent which has the advantages of prolonged duration of action, minimal evidence of renal vasoconstriction, no detrimental alterations in cardiac rhythmicity, and no appreciable change in cardiac output. All of these properties indicate that this agent may have practical application in the treatment of hypotensive states of many origins.

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THE IMAGE SURFACE OF A HOMOGENEOUS TORSO

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ABSTRACT

The image surface is a geometric representation of the relationship between a fixed-position current dipole inside a volume conductor and the electric potential it produces on the boundary of the conductor. It is a powerful means of conveying a wealth of information concerning some basic problems in electrocardiography, in terms of familiar heart-vector projection ideas. It gives deep insight into the nature of the relationship between torso surface voltages and the internal heart generator. A detailed image surface is presented in quantitative terms for a specific human torso shape and dipole position in order to illustrate its remarkable properties. Applications to the frontal-plane, Wilson central-terminal voltage and spatial vectorcardiography systems reveal shortcomings of current practices. Examples of possible research investigations suggested by the image surface are presented.

INTRODUCTION

RECOGNITION that the electrical manifestations of heart action are appreciably distorted as measured at the body surface of the human subject[1-5] is an encouraging trend in electrocardiographic research. Quantitative investigations of the types and degree of distortion are bound to lead to a more objective, precise and, therefore, more valuable interpretation of the electric potential differences which are produced at the body surface by electrical activation of heart muscle. Many factors are believed to be responsible for the distorted "electrical view" of the heart, such as shape and proportions of the human torso, inhomogeneities of the conducting medium, distributed nature of the electrical forces in the heart, electrical position and orientation of the heart, and others. However, quantitative data regarding the relative importance of these factors have not been firmly established.

The electrical system comprised of the heart and body is too complicated to be understood in its entirety at the outset. It is fruitful, however, to first introduce simplifications and then to relax them gradually. This has been the history of the development of many fields, electrocardiography not excepted. In this fashion, the ultimate goal of understanding all of the major factors which influence the system and their relative importance can be approached steadily.

In this spirit it has been assumed for the purposes of the present study that the heart may be represented by a fixed-position, variable-moment current dipole and that the body is a homogeneous, resistive conducting medium. It

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has been possible to investigate quantitatively the influence of torso shape and dipole position on the unipolar electric potentials at the torso surface, using accurate models of the human torso filled with tap water in which a small finite dipole is inserted in various positions occupied by the heart volume. Since the magnitude and direction of the dipole which produces these potentials is completely known in the torso, a direct comparison between results measured at the torso surface with the actual situation inside can be made.

The results which have been obtained using male and female torsos of widely different proportions and contour, and using a wide variety of dipole positions, show pronounced deviations from those which would be expected from current practices in electrocardiography.[5-7]

There are many specific and detailed ways in which the shortcomings of frontal-plane, unipolar and spatial electrocardiography can be presented. The most general and all-inclusive manner of portraying the results is in terms of the image surface, a geometric concept introduced by Burger and van Milaan (Part III).[1] The image surface is a powerful means of conveying a great amount of information giving deep insight into the problems faced in electrocardiography and, fortunately, it can be understood relatively easily. The image surface of a male torso model with a heart dipole located in the center of the ventricular mass is presented in detail here as an illustration. From the image surface one may deduce, in quantitative graphic terms, defects of frontal-plane electrocardiography as presently practiced, departure of the Wilson central-terminal voltage from the dipole mid-potential, errors of any of the various systems of spatial vectorcardiography, effects of dipole eccentricity, and others. Moreover, the image surface suggests a variety of lines of investigation which may be effectual in ultimately decreasing the amount of empiricism in present-day electrocardiography. It should be emphasized, however, that the surface presented here pertains to one specific torso shape and dipole position, both of which factors have a quantitative influence on the image surface. Any qualitative conclusions reached, however, may be expected to be generally useful for both male and female torsos. While typical distortion traceable to boundary shape and dipole position is revealed, the accuracy of the deductions made from torso image surfaces as applied to the human subject depends, of course, on the degree to which other factors not taken into account come into play in the human system.

THE IMAGE SURFACE

The image surface is a geometric representation of the relationship between torso surface voltages and an immersed current dipole which may be defined in words quite simply (see Appendix for a mathematical definition). For every point on the physical torso surface there is a corresponding point on the image surface which has the following property: The projection of the heart dipole onto the vector from the origin to a point on the image surface, multiplied by the length of this vector, gives a result which is proportional to the true unipolar potential measured at the corresponding point on the torso surface.* This vector-projection property holds for every point on the image surface and

*It is implied, of course, that the same dipole is considered for both the physical and image surfaces.

defines completely what is meant by the image surface. The same image surface is applicable for any strength and orientation of the fixed-position heart dipole.

It follows from this definition of the image surface that potential differences can also be handled. Consider any two points on the physical torso and the two corresponding points on the image surface. The projection of the heart dipole onto the vector joining the two image points, multiplied by the length of this vector, gives a result which is proportional to the potential difference measured at the corresponding two points on the torso surface.

The relationship between torso surface points, where vector projection ideas are invalid, and the corresponding points in image space, where vector projection can be applied, is shown geometrically by the image surface. The fact that the image surface differs markedly from the physical torso surface is immediate, graphic evidence of the substantial errors entailed in all systems of electrocardiography which apply vector projection to the physical surface.

METHOD

The experimental apparatus and method used in conjunction with the life-size, accurate homogeneous torso models of the human subject have been described in detail.[8-10] For this particular study the finite dipole was fixed in the center of the region occupied in life by the ventricular mass during very deep inspiration, and true unipolar potentials were measured at 192 points on the torso surface for various dipole orientations (see Appendix). These points are indicated in Fig. 1 which is drawn to scale. The numbers designate twelve parallel, equispaced transverse levels with 2-inch spacing between levels. Level 6 coincides with the heart center. Sixteen letter designations (A through P) indicate the intersections with each transverse level of radial lines separated by equal angles of 22½° emanating from the longitudinal anatomic axis of the torso. Thus, potentials were measured at 16 equiangular points around the trunk at each of twelve parallel, equispaced levels. Coefficients were determined for each of these points in order to determine the image surface, as described in the Appendix. All coefficients were determined independently at least twice for reliability.

RESULTS

It is difficult to portray a clear picture of the three-dimensional image surface because of its odd shape and unevenly stretched surface. However, one satisfactory method is to draw each of the twelve loops (which are in parallel, equispaced planes on the torso) as they appear in image space with reference to the same rectangular coordinate system shown in Fig. 1, the origin of which is the heart center. Three projections, in relative units, of each of the twelve loops in image space, which reside on the image surface, are given in Fig. 2 along with points corresponding to the angular intersections designated on the physical torso surface. The marked difference between the image surface and the physical torso surface is immediately evident. Several salient features of the image surface are mentioned below.

The major portion of the image surface corresponds to regions between levels 4 and 8 on the torso surface. A unit area on the anterior chest of the

torso is greatly magnified on the image surface as compared with unit areas near the lower parts of the trunk or regions around the shoulders and neck. This bears out the well-known fact that precordial electrode placement is very critical. The heart dipole tends to cause a bulging outward of the image surface for the nearer portions of the physical surface. The torso dipole is forward and toward

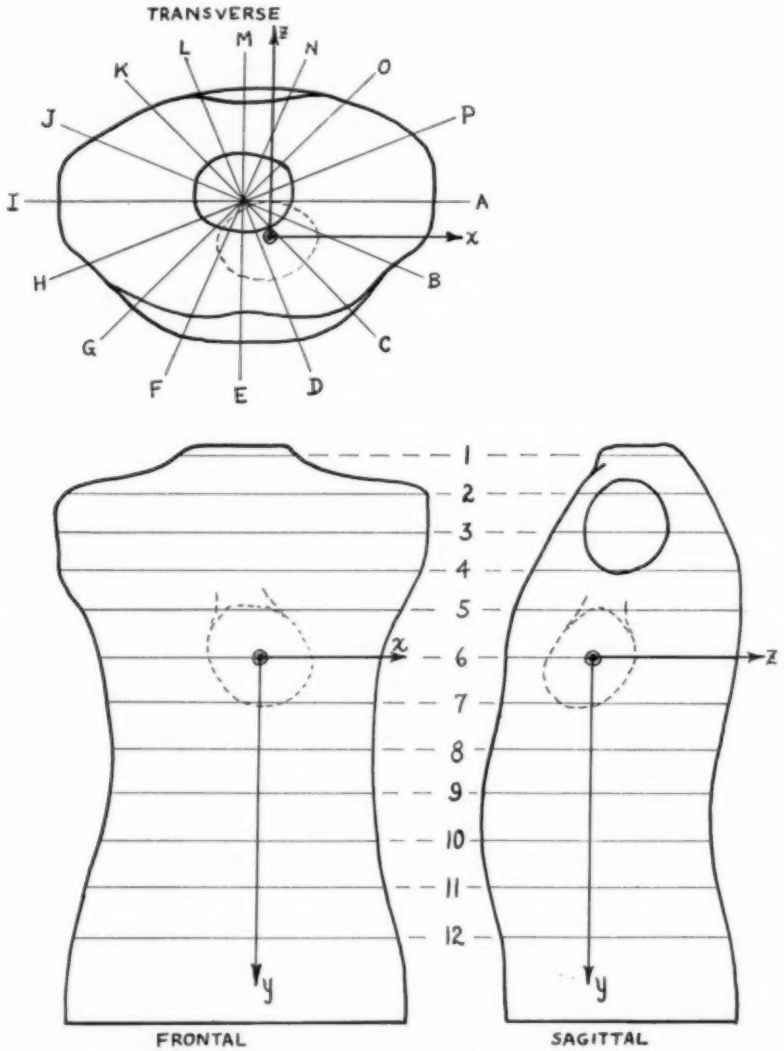

Fig. 1.—Scale drawing of three projections of the male torso model whose image surface is given in Fig. 2. The origin of a rectangular coordinate system is placed at the center of the ventricular mass. The x-axis is directed from right to left, the y-axis is directed from head to foot and the z-axis is directed from chest to back. The frontal plane is parallel to the xy-plane, the sagittal plane is parallel to the yz-plane, and the transverse plane is parallel to the xz-plane. Electrode positions on the torso surface are designated by two quantities: the level (numbers *1* through *12*) and the angle in the transverse plane (lettered *A* through *P*). The levels are each separated by 2 inches, with level *6* passing through *0*, while the angles are each equal to 22½°. Each of the 192 torso surface points (16 angle intersections at each of twelve levels) is shown in the corresponding frontal, sagittal, and transverse views of the image surface in Fig. 2. The torso was moulded on a male subject of the following description: height, 5 ft. 10½ inches; weight, 175 lbs.; chest, 38 in.; waist 33½ in.; hips, 36 in. The dipole was placed approximately 4 cm. in front of the plane parallel to the xy-plane passing through the centers of the right and left arm pits, approximately 2.5 cm. to the left of the plane parallel to the xz-plane passing through the torso midline, and approximately at the level between the fourth and fifth intercostal spaces.

the left; hence, the image surface is bulged out in that direction. This effect is very pronounced; for example, in the frontal view of the torso the dipole is located approximately 43 per cent of the transverse diameter of level 6 from the left side, while in the frontal view of image space, the dipole is located approximately 37 per cent of the transverse diameter of level 6 from the right side. As a consequence of the eccentric location of the heart, the physical back of the torso is contracted and distorted as it appears on the image surface. It may also be seen that the neck is not directly over the hips in image space. The twelve levels are far from parallel to each other in image space and do not lie in planes. Also, the equal angles between the radial lines in physical space are greatly distorted in image space, being highly magnified across the anterior chest and very much diminished in regions of the back. There are many other general features of this surface which the reader will undoubtedly discover on closer examination. Those mentioned should suffice to point out some of the major properties.

APPLICATIONS

The wealth of information conveyed by the image surface is rather startling. It sheds light on many basic questions in electrocardiography. It is so powerful a light that it will doubtless cause many factors hitherto obscured in the shadows to be shown up clearly. A representative group of applications of the information embodied in Figs. 1 and 2 will be given here by way of illustration.

1. Equipotential Extremities.—The extremities can be seen to be substantially equipotential surfaces in comparison with the rest of the torso surface, as has been well known from direct measurements on human subjects. The evidence for this is the small magnitude of the vectors in image space which join various points on the neck (about 1 inch above level 1), the hips (level 12), the right arm (2-I, 3-I, and 4-I) and the left arm (2-A, 3-A, and 4-A). These results show that the omission of the extremities in the torso model introduces very small errors.

2. The "Frontal-plane" Triangle.—The triangle formed by the right arm, left arm, and left leg for which vector projection is valid is given in image space by joining with vectors the points 3-I, 3-A (the average arm points) and the average of 12-N and 12-C. This triangle, shown in red in Fig. 2, can be seen to depart drastically from the equilateral triangle of Einthoven and associates[11]: The sides of the triangle are unequal. (The distance from 3-A to 3-I is 82 units, 3-A to the average of 12-N and 12-C is 184 units, and 3-I to the average of 12-N and 12-C is 152 units). The plane of the triangle is not parallel to the frontal plane. (It tilts backward and toward the left.) The heart dipole lies considerably forward of the plane of the triangle.

A detailed study of the significance of these discrepancies is presented elsewhere,[5] the most glaring of which is the elongation of the triangle in the head-to-foot direction. This means that the head-to-foot component of the dipole is approximately one-half the size that has been supposed heretofore, based on torso shape and dipole position only.

3. Wilson Central-terminal Voltage.—The Wilson central-terminal voltage can be obtained in image space by projecting the heart dipole onto a vector extending from the origin to the median point of the "frontal plane" triangle,[7] shown in Fig. 2 in red. The length of this vector for the image surface of Fig. 2

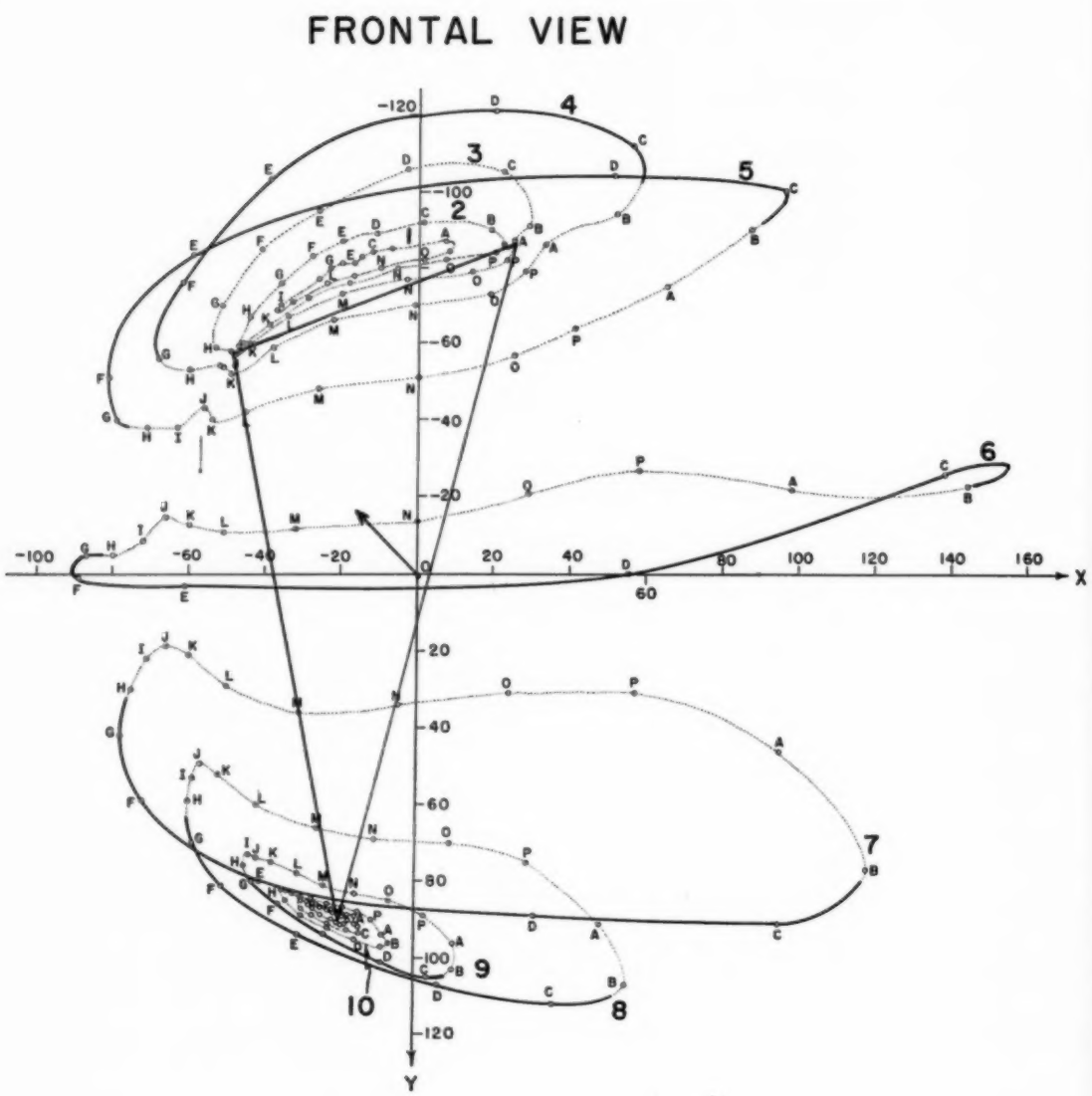

Fig. 2, *A*.

Fig. 2.—Frontal (*A*), sagittal (*B*), and transverse (*C*) views of each of the twelve loops on the physical torso as they appear on the image surface. The 16 points (*A* through *P*) on each loop correspond to the angle intersections with the corresponding levels on the physical torso. Solid lines indicate portions of the loops which lie in front of the plane of the paper. The limb-lead triangle is shown in red in each view as is the Wilson central-terminal vector, directed from the dipole center *O* to the median point of the limb-lead triangle. See text for discussion and applications.

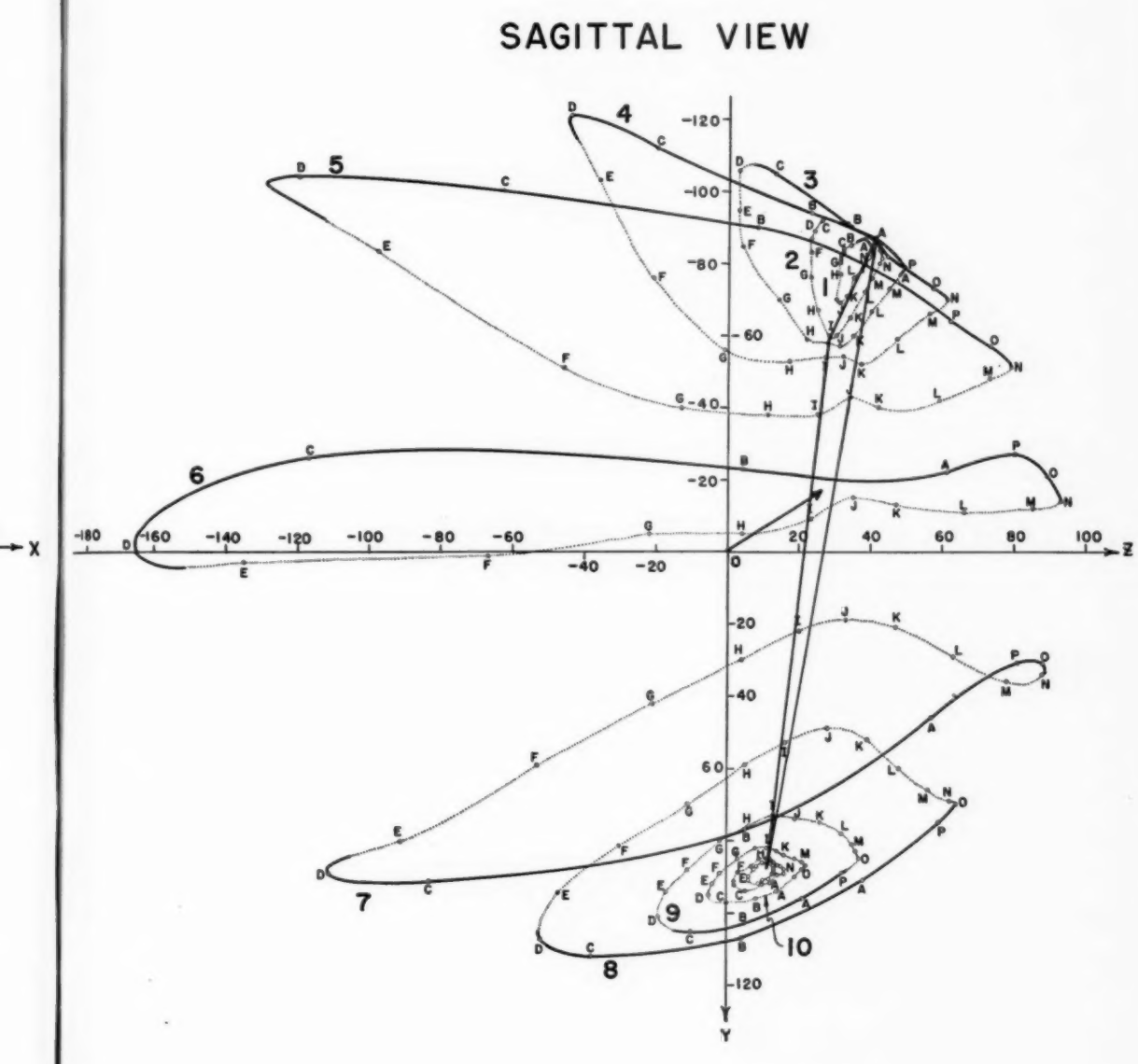

Fig. 2, *B*. *(For legend see opposite page.)*

is 34 units, and it is directed upward and toward the back. This vector is about 20 per cent of typical precordial electrode unipolar vectors (from the origin to 6-D, for example) and about 35 per cent of typical unipolar limb electrode vectors (from the origin to 3-A for the left arm, for example), and gives insight into the size of the Wilson central-terminal variations in comparison with the true unipolar voltages. However, the heart dipole variations must also be included to obtain an accurate estimate, because the Wilson central-terminal vector direction is generally quite different from those of the other vectors being considered.

A detailed study of the behavior of the Wilson central-terminal for this dipole position as well as many others in both male and female torsos is presented elsewhere.[5]

4. Systems of Spatial Vectorcardiography.—Any system of spatial vectorcardiography may be analyzed in terms of the image surface of Fig. 2. If the specific electrode positions desired do not fall exactly on the points in Fig. 2, an estimate of their locations by interpolation may be made from nearby points. As an example, the tetrahedron of Wilson and associates[12] can be located on each of the three views of Fig. 2 by joining points 3-I, 3-A, the average between 12-N and 12-C, and the point about midway between 6-M and 6-N. It is clear, if this is done, that the tetrahedron so constructed is not equilateral and, moreover, that the heart dipole is not located within the tetrahedron. As another example, it can be seen that the electrode arrangement of Duchosal and Sulzer[13] (10-J, 10-G, 10-P and 2-K) departs drastically from the "double cube" presumed to exist; furthermore, the heart center is far from equidistant from these points in image space. The system of Grishman and Scherlis[14] can be seen to possess comparable defects, using the image surface of Fig. 2. These matters have been discussed in detail.[6] It should be clear that most of the presently employed systems of vectorcardiography entail very sizeable errors even if torso shape and dipole position only are considered.

There are many ideas suggested by the image surface which could serve well as a basis for future research. A few of these are given below as illustrations:

1. Improved central terminal: If an improved central terminal using three electrode positions is devised, it can be seen from the image surface and the geometric interpretation of the central-terminal vector which has been presented that the plane containing the three points on the image surface should also contain the origin O of image space. If this is the case, then a suitable choice of three resistors could lead to a perfect central terminal, in principle. Furthermore, a study of the image surface reveals that a central terminal may be formed which is at the same potential as the mid-potential of the dipole by connecting only two resistors to two body-surface points such that the line joining the corresponding points on the image surface passes through the origin in image space. Two unequal resistors of ratio equal to the geometric distances from the image points to the origin would be required.

An investigation of these possibilities, of which there are an infinite number of combinations, could lead to a central terminal which approximates the dipole

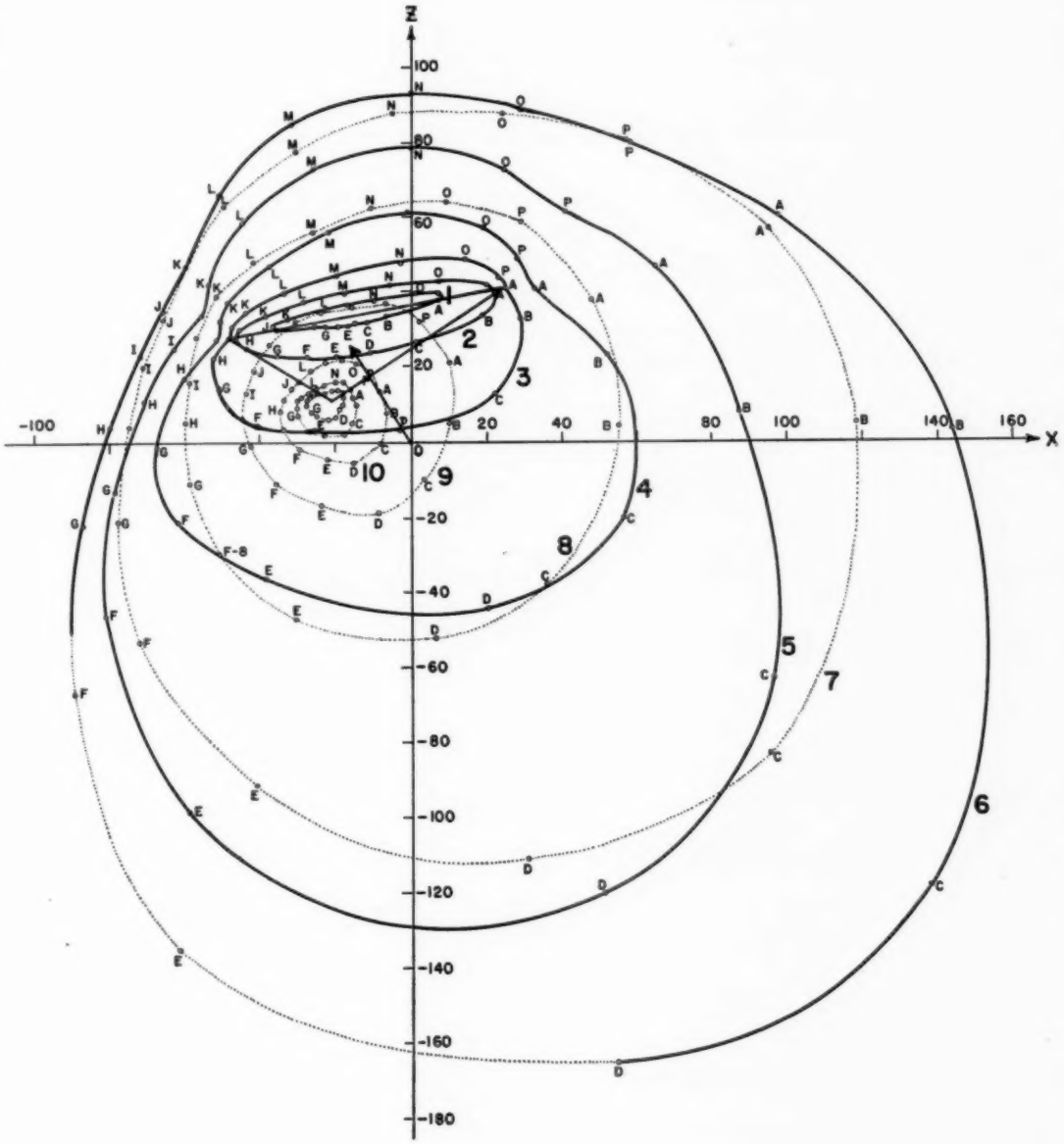

Fig. 2, *C*. (*For legend see page 762.*)

mid-potential to a better degree than those presently employed. The choice of an improved central terminal must, of practical necessity, favor electrode positions which are least susceptible to variations of the image surface among individuals, traceable to different heart positions, body builds, and different inhomogeneities. In principle, the heart dipole variations can be determined completely from three independent bipolar measurements, and a central terminal is not essential.

2. *Improved electrode positions for spatial vectorcardiography*: A study of the image surface reveals that it is possible to find pairs of points on the torso which will have potential differences proportional to only one component of the heart dipole. Such points would appear to provide the simplest basis for a rational system of vectorcardiography. Of the infinite number of available choices, it should be possible to determine the most practical arrangement for use on the human subject by direct experimentation. As an illustration of how such electrode positions can be selected, suppose it is desired to find a pair of electrodes which yield a potential difference proportional only to the head-to-foot (y-axis) component of the dipole. Pairs of points where any of the loops cross one another in the transverse view of Fig. 2 are suitable. For example, 10-N and 2-E, or 8-M and 4-M, are two possible electrode pairs which display a potential difference proportional to p_y only. The relative amplitudes for these points can be obtained from either of the other two views of the image surface by measuring the distances between these points. For example, the first pair will yield a larger voltage than the second pair in the ratio 22.0/16.8, but the wave form would, presumably, be the same and directly proportional to the y-component of the heart dipole. An accurate comparison of wave shapes for such pairs of points using both distant and precordial electrode positions on the human subject should provide some revealing information concerning localized effects in precordial leads owing to the proximity of the heart to the chest wall. There is a growing amount of evidence which indicates that these local effects may not be as large as it has been supposed in the past.[4,15]

3. *Studies of dipole and homogeneity approximations*: The image surface enables indirect studies of the validity of the assumptions of a fixed dipole representation of the human heart and of a homogeneous conducting medium; i.e., of the applicability of the torso model image surface to the human subject. If body surface voltages on a human subject (whose torso image surface is known from homogeneous torso model measurements using a dipole located in the point corresponding to the center of the subject's heart) are recorded and compared with the results expected from the image surface, the degree of agreement is a quantitative measure of the validity of these assumptions. Such studies are currently in progress in this laboratory. The mirror-pattern studies of Schmitt and associates[4] tend to support the validity of the dipole approximation, even in many subjects with heart disease. Theoretical evidence[15] also tends to lend some credence to the dipole approximation. With the use of the torso image surface it is possible to obtain a quantitative measure of these relatively unexplored but commonly used approximations.

The power of the image surface and the insight it gives into problems in electrocardiography are remarkable, as has been illustrated by only a few of the many possible applications. That there is much room for improvement over current practices is clear. However, it should be remembered that the image surface is quantitatively dependent upon dipole position and torso shape and also rests upon the assumption of a fixed-position dipole representation of the human heart. Therefore, the quantitative data presented here should be applied cautiously until further information is obtained concerning the applicability of the underlying assumptions to the human subject. Nevertheless, it is clear that the image surface presented here, which takes torso shape and dipole position into account, provides a substantially more accurate basis for electrocardiography than afforded by presently used theories based on a spherical torso with a centric dipole, which can be seen to be erroneous.

SUMMARY

1. The geometric concept of the image surface of a bounded volume conductor in which a fixed-position current dipole is immersed is defined in terms of vector projection.

2. A homogeneous male torso with a heart dipole in the center of the ventricular mass serves as a detailed illustration of a typical image surface, using 192 points on the surface.

3. Extreme distortion of the image surface as compared with the physical torso surface is shown. The difference in shape, unequal stretching, bulging on the regions closest to the heart, and so forth are pointed out.

4. Typical applications of the image surface to quantities used in electrocardiography are illustrated for the limb-lead triangle, Wilson central-terminal voltage, and systems of vectorcardiography. Major errors of current practices are revealed.

5. Examples of certain lines of electrocardiographic research which are believed to be fruitful are suggested by nature of the image surface.

It is a pleasure to acknowledge the interest shown by Dr. C. F. Kay. The facilities provided by Dr. L. G. Thomson during the course of this study were especially helpful and are gratefully appreciated.

APPENDIX

The potential produced by a fixed-position, variable-moment current dipole at an arbitrary point within an inhomogeneous, linear electrical conducting medium can be expressed as[7]

$$V = \vec{c} \cdot \vec{p} = c_x p_x + c_y p_y + c_z p_z$$

where V is the potential difference between a point in the medium and the dipole mid-potential, arbitrarily assigned the value zero; p_x, p_y and p_z are the rectangular components of the fixed-position, time-varying current dipole vector $\vec{p}$; and c_x, c_y and c_z are the components of a vector $\vec{c}$ which are real functions in the case of a resistive medium and which depend upon the characteristics of the medium (size, shape, resistivity, distribution of inhomogeneities), the dipole position, and the location of the point of potential V. For a designated medium, dipole position and boundary point, the vector $\vec{c}$ is constant, and V can be obtained by projecting the time-varying vector $\vec{p}$ onto the fixed-vector $\vec{c}$ and then multiplying by the magnitude of $\vec{c}$. A point on the

image surface is defined as the tip of the vector $\vec{c}$, where $\vec{c}$ originates from a point corresponding to the dipole mid-potential. The entire image surface is the locus of all possible values of $\vec{c}$ for a designated medium and dipole position.

The three components of $\vec{c}$, and hence a point on the three-dimensional image surface, were determined experimentally for each boundary electrode position by aligning the dipole, sequentially, along the x, y and z axes, measuring the potentials at a given boundary point for each orientation. When $\vec{p}$ is aligned entirely along the x-axis, p_y and p_z are zero so that the potential is proportional to c_x; similarly, with $\vec{p} = \vec{j}p_y$ and $\vec{p} = \vec{k}p_z$, V is proportional to c_y and c_z, respectively. The dipole position was, of course, held constant despite the changes in orientation. The image surface was determined to an accuracy of approximately 5 per cent.

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DEPOLARIZATION OF THE VENTRICLE WITH BUNDLE BRANCH BLOCK

Studies on the Mechanism of Ventricular Activity. X.

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EARLIER concepts concerning the electrocardiographic diagnosis of bundle branch block stem from the studies of Eppinger and Rothberger in 1910[1] and Lewis in 1915.[2] For more than 20 years, the experimental observations of these workers were generally assumed to apply to limb-lead tracings from man. Evidence inconsistent with the prevailing criteria for differentiating clinical disorders of the left and right bundle branches was reported by Barker, Wilson and associates in 1929 and 1931.[3,4] Not until 1932, however, when Wilson applied the technique of precordial-lead electrocardiography, was it conclusively established that clinical disturbances formerly classified as left bundle branch block actually involved the right branch and vice versa.[5]

The abnormally large positive complexes recorded over ventricles with bundle branch block have been explained by extending Bernstein's membrane theory to cardiac muscle. Depolarization of the ventricular myocardium is represented as an advance of dipoles, the positive pole preceding and the negative pole following the activation front. In left bundle branch block, activation of the septum presumably occurs from right to left. Hence the left ventricular cavity faces the positive side of the septal activation front and therefore presents a positive potential. This potential is transmitted through the cavity and left ventricular wall, causing an R wave in epicardial and precordial leads. After the septum is depolarized, delayed activation of the left ventricular wall occurs from endocardium to epicardium. The left ventricular surface then faces the positive side of the intramural activation front. A second positive component (R′ wave) thus appears in the epicardial and precordial leads. Conversely, in right bundle branch block, the first component of the large positive complex over the right ventricle is believed to represent activation of the septum from left to right, while the second component represents delayed activation of the right ventricular wall.

As discussed in previous papers,[6,7] electrical activity throughout the normal ventricles has been studied by means of a specially designed plunge electrode.

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The distribution of potentials was found to conflict in certain respects with classic theory concerning the manner of ventricular activation. In the present study, techniques similar to those used in normal hearts have been applied in bundle branch block. Depolarization potentials recorded throughout the wall and cavity of ventricles with bundle branch block are described in this paper. A subsequent paper concerns the electrocardiographic changes associated with myocardial infarction in ventricles with bundle branch block.

MATERIALS AND METHODS

In each of forty-five dogs, bundle branch block was produced by cutting the left or right septal surface with an iridectomy knife passed through the appropriate auricle and auriculoventricular valve or plunged through the lateral base of the ventricular wall. Epicardial, intramural, intraseptal, and intracavity leads were then obtained by methods similar to those used in a previous investigation of normal hearts.[6,7] Simultaneous intramural leads from the subepicardial and subendocardial regions were registered with a "compound" electrode consisting of two plunge electrodes of different lengths. In most experiments, one or two compound electrodes were sutured in the wall at locations varying from base to apex. Occasionally, three electrodes were placed in different parts of the same ventricle.

Electrocardiograms were registered on a dual-channel Brush recorder at a paper speed of 125 mm. per second and on a photographic-writing Sanborn Twin-Beam at 75 mm. per second. Because of its more rapid recording rate, the Brush instrument yields complexes which can be timed with greater accuracy. The Sanborn Twin-Beam, on the other hand, is more sensitive and is therefore superior for analyzing configurations. In order to check the accuracy of the results, a DuMont cathode-ray oscillograph (Type 322A) with a Fairchild Oscillo-Record camera was used in several experiments. The same conclusions were reached whether the Brush recorder, the Sanborn photographic-writing electrocardiograph, or the cathode-ray oscillograph was employed.

RESULTS

As reported elsewhere,[6,7] the depolarization complexes recorded from the dog's ventricles during normal intraventricular conduction are as follows: the epicardial surface and immediately subjacent myocardium yield predominantly positive deflections of the Rs type. In intramural leads from progressively greater depths of the ventricular wall, the R wave becomes smaller and the S wave grows larger. When the subendocardial zone is reached, purely negative deflections are inscribed. Pure QS waves occur in leads from all portions of the mural endocardium and within both ventricular cavities except the right cavity near the septum where an rS wave appears. In general, predominantly negative depolarization complexes are obtained throughout the ventricular walls and cavities except in a thin epicardial shell comprising approximately one-fourth the thickness of the mural myocardium.

Cavity of the Ventricle With Bundle Branch Block.—As in normal ventricles, leads from different portions of the cavity in "blocked" ventricles exhibited depolarization complexes of different magnitude and configuration. The deflection most frequently recorded within the cavity of either the left or right ventricle with bundle branch block consisted of a large R wave followed by a small S component (Fig. 1,*A*). Somewhat less commonly, pure R waves were obtained (Fig. 1, *B*). These findings conflict with the prevailing concept,[8] based upon observations by Wilson and associates[9] and Sodi-Pallares and co-workers,[10] that an S wave equal to or greater than the R wave is registered in cavity leads from ventricles with bundle branch block.

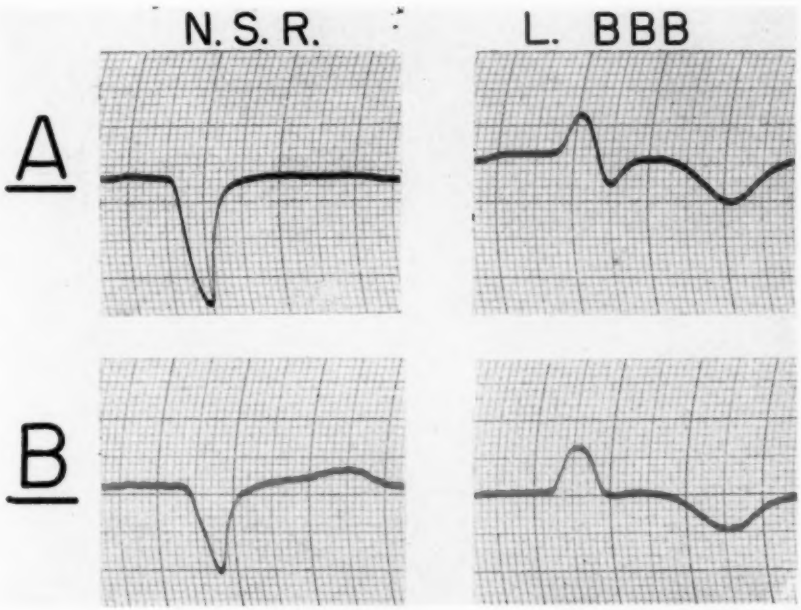

Fig. 1.—Leads from within left ventricular cavity registered on Brush recorder during normal conduction (left-hand tracings) and after production of left bundle branch block (right-hand tracings). Paper speed 125 mm. per second. *A*, Case 1. The normal intracavity QS wave changed to an Rs deflection after bundle branch block was produced. *B*, Case 2. In this instance, the cavity presented a pure R wave after the bundle branch was blocked.

On ten occasions, the normal intracavity QS wave changed to an RS deflection after an attempt was made to produce bundle branch block by means of a transverse incision across the septum. When the degree of bundle branch block was increased by inflicting a second incision in the septum, the intracavity complex became entirely or almost entirely positive. In four other instances, a longitudinal cut parallel to the bundle was made on the left side of the septum and the presence of segmental block established by surface exploration.[11] Limb lead tracings exhibited slight widening of the QRS complex, while the left cavity yielded a tiny rs wave (Fig. 2, *B*). Complete block was then produced by means

of a second cut perpendicular to the longitudinal incision and extending across the left bundle branch; the intracavity deflection changed to a pure R wave (Fig. 2, *C*). In two animals, the intracavity complex decreased in size but remained purely negative after small segments of the right ventricle were blocked (Fig. 3, *B*), then changed to an RS wave when larger segmental blocks were produced, and finally became predominantly positive after complete right bundle branch block was obtained (Fig. 3, *C*).

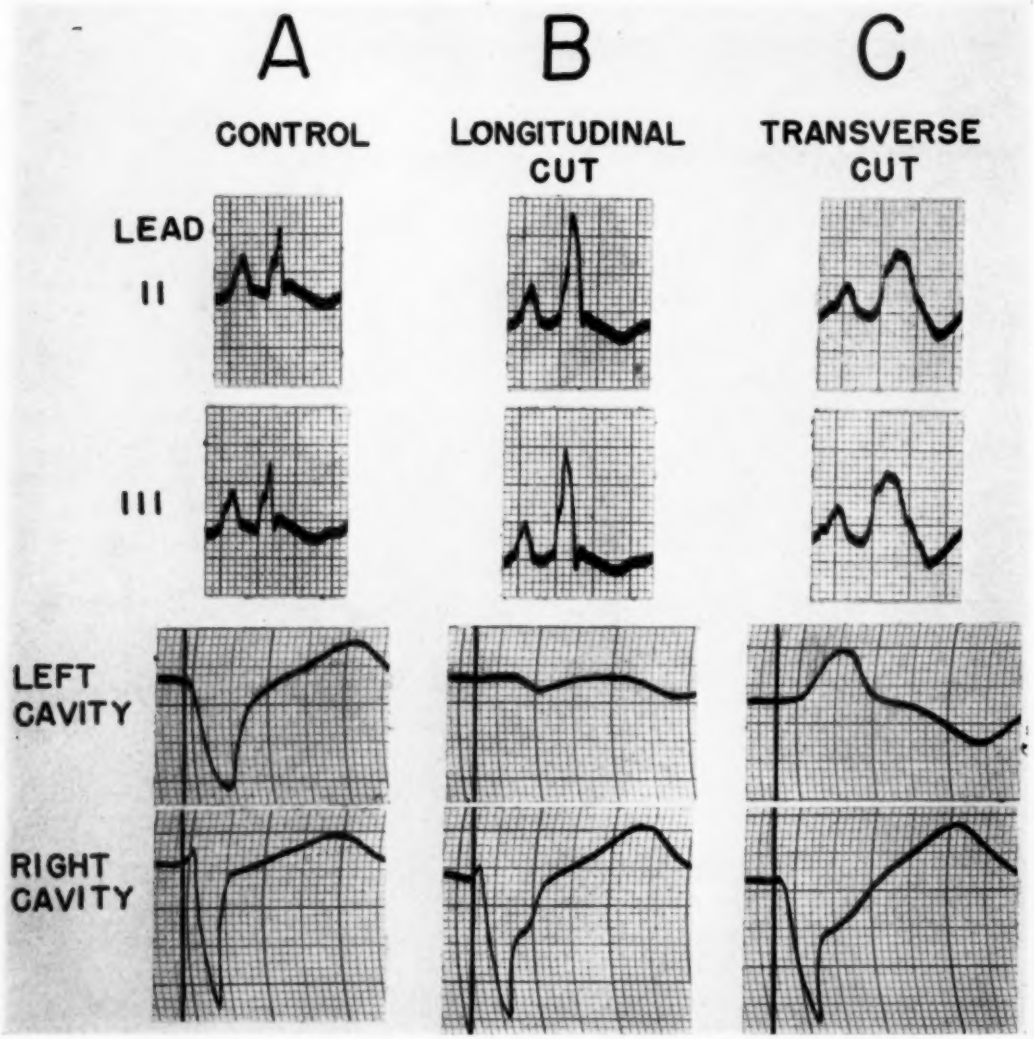

Fig. 2.—Limb and intracavity leads recorded before and after production of left bundle branch block. Limb leads registered on Sanborn Polyviso at 50 mm. per second and cavity leads on Brush recorder at 125 mm. per second. *A*, Normal intraventricular conduction. Left cavity yields pure QS wave. *B*, After longitudinal cut on left side of septum. The presence of segmental block was established by epicardial tracings as well as by widening of the right cavity complex and characteristic changes in Leads II and III. The cavity of the left ventricle presents an RS wave of low amplitude. *C*, Degree of block has been increased by inflicting a second cut perpendicular to the first incision. Limb lead changes and widening of right cavity complex are more pronounced than in *B*. A pure R wave is registered from the left cavity.

On the basis of the preceding observations, the conclusion was reached that the cavity of ventricles with complete bundle branch block characteristically yields a purely positive complex or a large positive followed by a small negative wave. Only if the bundle branch is incompletely blocked does the cavity present a large negative deflection. Segmental block, a form of incomplete bundle branch block,[11] usually exhibits rS waves but occasionally shows pure QS waves of diminished amplitude in cavity leads. The cavity of the ventricle with bundle branch

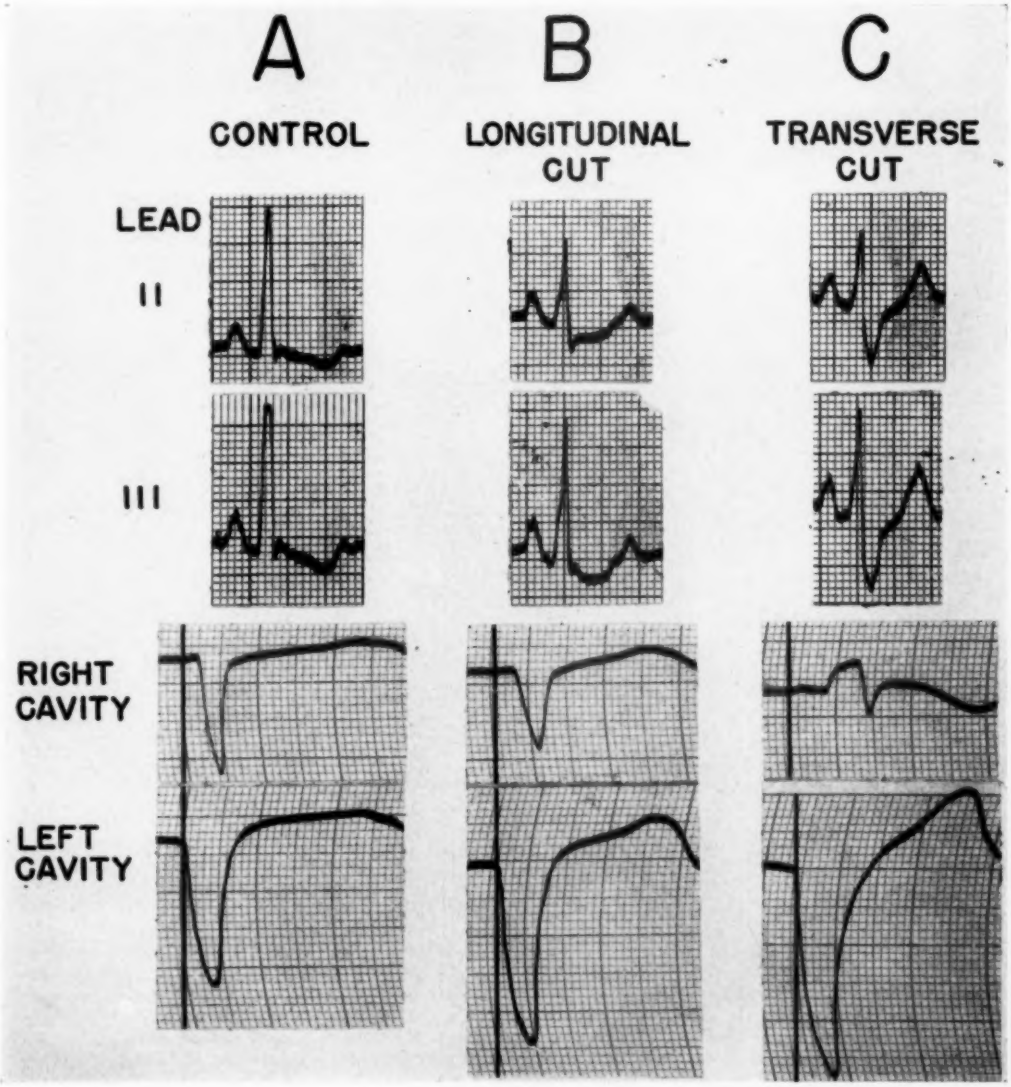

Fig. 3.—Limb and intracavity leads before and after production of right bundle branch block. *A*, Normal intraventricular conduction. *B*, Segmental block, as established by epicardial tracings, occurred when longitudinal incision was made in right side of septum. The right cavity complex remained negative but decreased considerably in amplitude. *C*, After second cut perpendicular to the longitudinal incision. Limb leads show typical right bundle branch block pattern. The right cavity now yields an Rs wave.

block thus may yield a variety of complexes including QS waves, rS waves, RS waves, Rs waves and pure R waves, depending on the type and degree of block.

Wall of the Ventricle With Bundle Branch Block.—In all forty-five experiments, single and simultaneous leads were recorded at all levels from epicardial surface to endocardium and at various locations from base to apex of the right or left ventricle with bundle branch block. The epicardial leads consistently presented abnormally tall, wide, notched or slurred R waves, occasionally followed by small s waves. A few epicardial tracings showed Rs deflections while simultaneous tracings from the underlying cavity exhibited pure R waves.

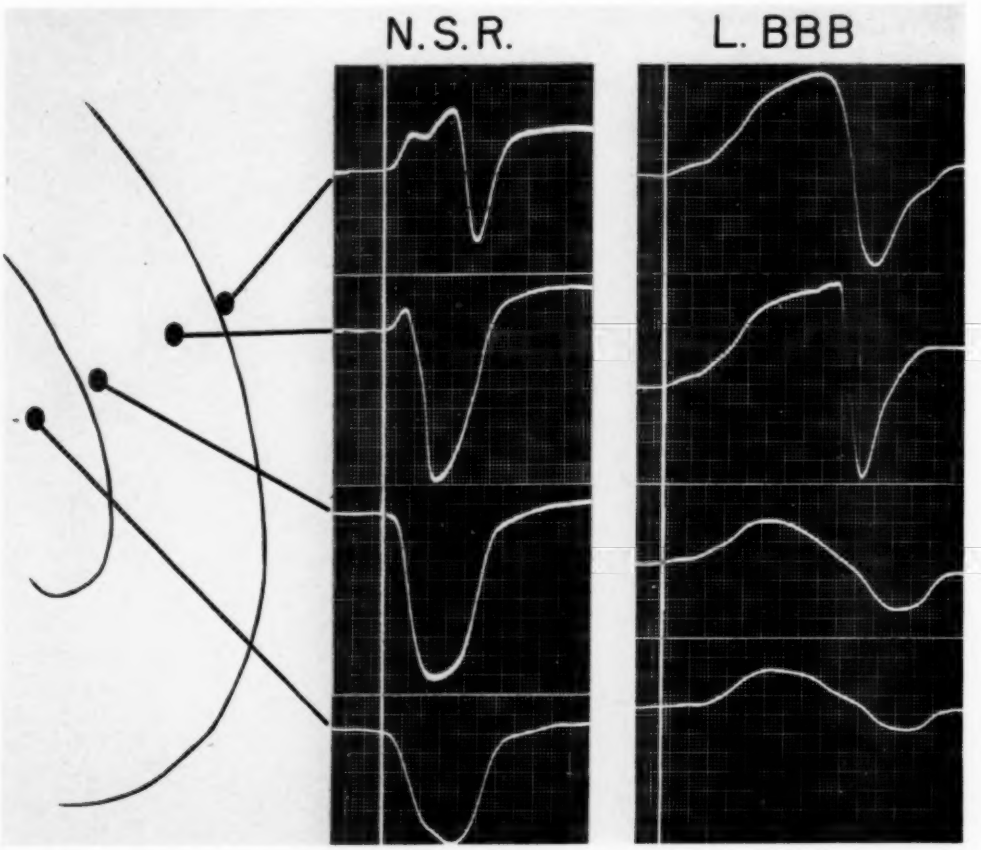

Fig. 4.—Epicardial, intramural, and intracavity leads from left ventricle recorded on the cathode ray oscillograph before and after production of left bundle branch block. One large box equals about 0.008 sec. Heavy vertical line is simultaneous reference for timing onset of complexes. During normal intraventricular conduction, the epicardium yields an RS wave while intramural and intracavity tracings present predominantly negative depolarization complexes. During left bundle branch block, all levels of the wall and cavity of the left ventricle are predominantly positive. Note that positivity begins in epicardial lead while cavity complex is isoelectric.

Several other ventricles yielded Rs complexes from both the epicardium and the cavity but the s component was significantly larger in the epicardial than in the cavity lead (Fig. 4). Hence the epicardial s wave in these instances apparently did not result from transmission of negative potentials through the cavity as is generally supposed.

Intramural leads from either the left or right ventricle with bundle branch block, like the epicardial leads, always contained abnormally large R waves sometimes followed by s waves. A gradual decrease in amplitude of the complex occurred as the electrode was moved from epicardium to cavity (Fig. 4). The large R waves recorded from ventricles with bundle branch block were similar to those obtained in epicardial and intramural leads from ventricles without block when extrasystoles and tachycardia were produced by stimulating the opposite ventricle.[12]

Source of the R Wave Over Ventricles With Bundle Branch Block.—As noted previously, the initial positivity recorded over ventricles with bundle branch block is generally believed to result from septal depolarization. Positive potentials arising in the septum presumably are transmitted through the cavity and wall of the ventricle to the overlying epicardium and precordium. Under such circumstances, the initial positivity (R wave) should begin simultaneously in cavity, intramural, and epicardial leads. Moreover, if the positivity arises in the septum, it should decrease in magnitude as the distance from the septum increases. In incomplete bundle branch block, the R waves were found to begin simultaneously in cavity, intramural, and epicardial leads, but, contrary to theory, increased in magnitude with the distance from the septum. In complete bundle branch block, the intracavity R wave began later than the R wave in leads from the outer layers of the wall and from the epicardial surface (Fig. 4). Thus the initial positivity recorded over ventricles with bundle branch block does not appear to be transmitted through the cavity and wall to the epicardium.

In order to further investigate this phenomenon, intraseptal leads were recorded simultaneously with cavity and intramural leads from ventricles with bundle branch block. While the greater part of the septum underwent activation, only a small portion of the cavity immediately adjacent to the septal surface exhibited slight positivity. Other parts of the cavity remained isoelectric. Significant positivity throughout the cavity did not occur until the extreme right side of the septum became activated almost simultaneously with the intramural myocardium of the right ventricle. In ventricles with bundle branch block, therefore, septal activation apparently contributes to the potential of only a small portion of the cavity adjacent to the septal surface. Even in this part of the cavity, the deflection resulting from septal activation is extremely small. The observation that septal potentials are not transmitted through the cavity has been made in normal ventricles[6] as well as in bundle branch block. It thus appears improbable that these potentials could contribute significantly to the complexes in intramural, epicardial, and precordial leads.

Direction of Depolarization in Ventricles With Bundle Branch Block.—Since the positivity recorded over ventricles with bundle branch block apparently was not significantly influenced by septal activation, it must have resulted primarily from depolarization of the wall. The abnormal size and shape of the R wave thus suggested that the wall must depolarize in an abnormal manner. An attempt was therefore made to determine if the direction of depolarization in ventricles with bundle branch block differed from that in the normal ventricle. The classic

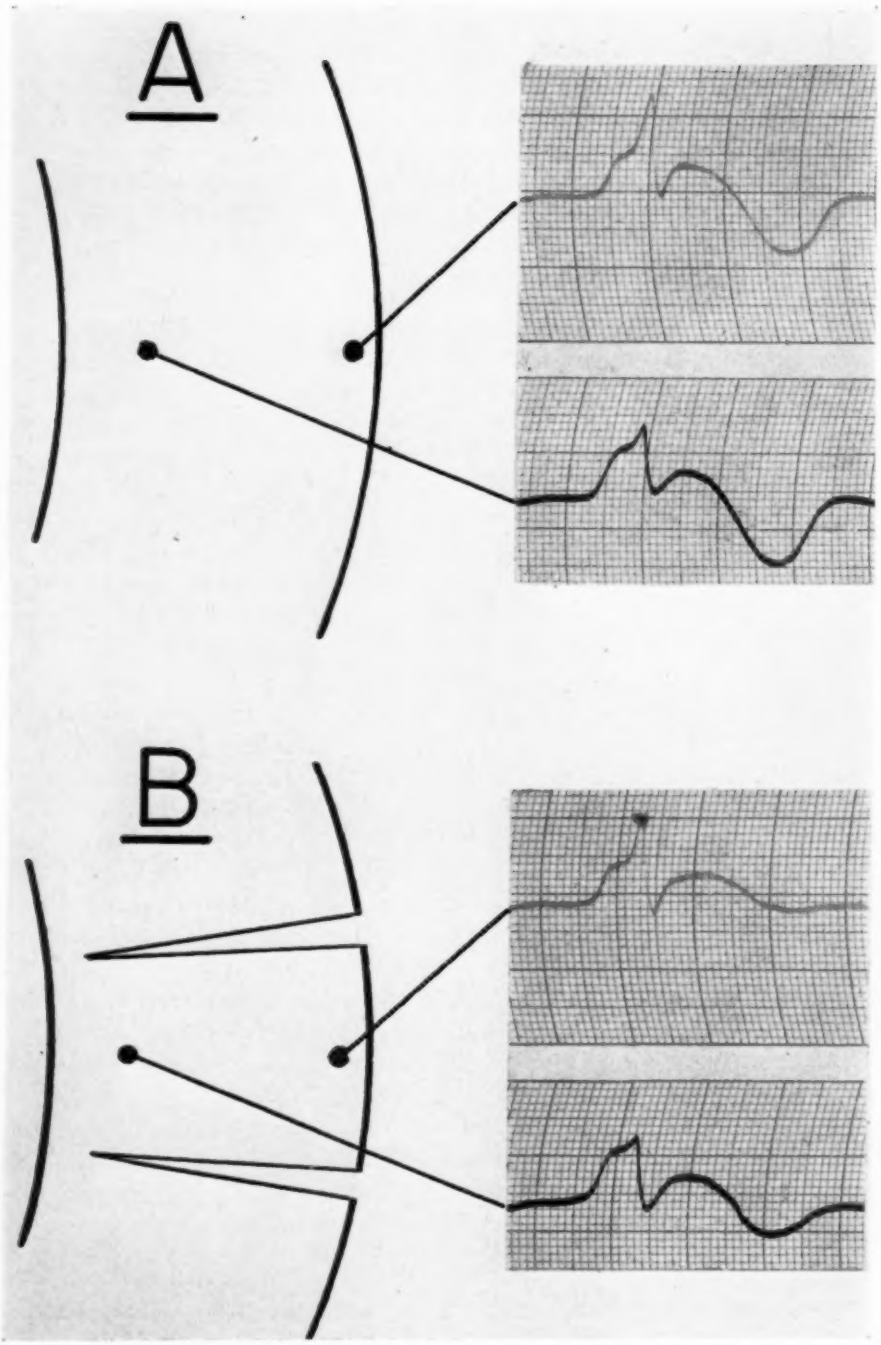

Fig. 5.—*A*, Simultaneous subepicardial and subendocardial leads from left ventricle during left bundle branch block. Registered on Brush recorder at 125 mm. per second. *B*, Same leads after region of the left ventricle containing the electrodes was isolated from surrounding myocardium. The complexes in *A* and *B* are essentially similar, indicating that the excitatory process did not pursue a lateral pathway through the ventricular wall. Note that R wave in subepicardial tracings is taller than in subendocardial tracings, but onset of the downstroke occurs almost simultaneously in the two leads.

method of timing the intrinsic deflections in multiple direct leads was first employed. For practical reasons, the onset of the downstroke was selected to represent passage of the excitation process beneath the electrode. The lower portion of the downstroke could not be timed as accurately because it was often distorted by currents of injury. In those tracings which showed no distortion, however, essentially the same results were obtained whether the onset, the termination, or the mid-point of the downstrokes was timed.

If depolarization of the ventricular wall progressed from endocardium to epicardium, the intrinsic deflection should appear earlier in subendocardial leads than in subepicardial leads. An examination of control tracings showed that this was consistently true during normal intraventricular conduction. In the same ventricle after bundle branch block was produced, the interval between the onset of the downstrokes in subepicardial and subendocardial leads was abnormally small and in some instances was imperceptible (Fig. 5). Although the R wave recorded from the subendocardial or midmural regions usually reached its peak slightly before the R wave from overlying subepicardial muscle, the reverse was true on some occasions. The timing of the intrinsic deflections thus failed to yield consistent results concerning the direction of depolarization in ventricles with bundle branch block. A more direct experimental approach to this problem therefore was employed as follows.

In each of six ventricles with bundle branch block, an intracavity lead was recorded simultaneously with subendocardial and subepicardial leads from superjacent sites. The region containing the plunge electrodes was then almost completely isolated from surrounding muscle by means of incisions extending from the epicardial surface to within 2 or 3 mm. of the endocardium. If the depolarization process pursued a lateral pathway through the ventricle, it would have been blocked by the incisions and its course radically changed. As illustrated in Fig. 5, intramural leads recorded from the isolated tissue consistently were identical with or only slightly different in timing and configuration from the control tracings, demonstrating that the incisions had little effect on the direction of the excitation process. In accordance with general belief, therefore, depolarization of the ventricle with bundle branch block apparently did take place from endocardium to epicardium.

DISCUSSION

According to classic theory, the abnormally large positive deflections recorded over ventricles with bundle branch block represent two vector forces, the first resulting from septal depolarization and the second from delayed depolarization of the underlying wall. In the present experiments, however, the initial positivity registered at the surface of ventricles with block apparently was not transmitted from the septum through the cavity. Therefore, depolarization of the wall alone appeared responsible for the large epicardial R waves of bundle branch block.

The epicardial R waves recorded over ventricles with block were considerably larger and different in configuration from those registered over normal ventricles. Since these abnormal complexes apparently result from mural depolarization, the wall of the blocked ventricle must depolarize in a highly abnormal manner.

This was further evidenced by the appearance of the cavity and intramural complexes. If mural depolarization occurred as a normal advance of dipoles, the intramural muscle activated first would present a negative potential after it underwent activation. Only in parts of the wall which depolarized last would positive potentials prevail. Relatively large negative deflections thus should occur in some intramural leads between the cavity and epicardium or between the base and apex regardless of the direction of depolarization. Moreover, a large negative wave should be registered from the cavity. Actually, however, purely or predominantly positive complexes were recorded throughout the wall and cavity of ventricles with bundle branch block.

The preceding observations suggest that the electrocardiogram of bundle branch block cannot be fully explained by the classic theory of abnormal septal depolarization followed by delayed mural depolarization. In addition to these factors, a marked change in the manner of depolarization appears to occur in the ventricle with block which is primarily responsible for the abnormal positivity recorded in cavity, intramural, epicardial, and precordial leads. Since similar complexes are obtained from ventricles without block when extrasystoles or tachycardia arise in the opposite ventricle, it is possible that the abnormality of mural depolarization relates to the abnormal route by which the depolarization process enters the wall. In normal hearts, the depolarization wave passes rapidly through the Purkinje system before entering the mural myocardium. In bundle branch block or in ventricular arrhythmias, on the other hand, the wave presumably crosses the septum and enters the mural myocardium directly without passing through the Purkinje system.

Although ventricles with bundle branch block apparently depolarize in an abnormal manner, they nevertheless were found to contract efficiently. High-speed cinematographs revealed that contraction occurs later in the ventricle with block than in the contralateral ventricle.[13] Except for this delay in contraction, the ventricle with block appeared to function normally.

SUMMARY AND CONCLUSIONS

1. Intramural and intracavity potentials in left and right bundle branch block have been studied by means of specially designed plunge electrodes.

2. Purely or primarily positive depolarization complexes were registered from all parts of the cavity in ventricles with complete bundle branch block. In incomplete block, the cavity yielded a variety of complexes ranging from QS waves of diminished amplitude to Rs waves. The size of the negative deflection appeared to vary inversely with the degree of block.

3. All parts of the wall of the ventricle with complete bundle branch block yielded predominantly positive depolarization complexes. The R waves were largest in leads from the epicardial surface and grew progressively smaller as deeper layers of the myocardium were explored.

4. Intraseptal, intracavity, intramural, and epicardial leads from ventricles with bundle branch block were compared with respect to timing and magnitude of the depolarization complexes. The results were inconsistent with the classic

theory that the initial portion of the R wave in epicardial and precordial leads results from transmission of septal potentials through the cavity and ventricular wall.

5. An attempt was made to determine the direction of depolarization in ventricles with bundle branch block by comparing the onset of the downstrokes in multiple intramural leads. Inconclusive results were obtained. The crude experimental method of recording intramural leads before and after isolating a portion of the wall indicated that depolarization occurred from endocardium to epicardium.

6. The large positive complexes recorded over ventricles with bundle branch block appear to result entirely from depolarization of the underlying wall. These complexes are abnormal in amplitude, width, and shape because depolarization of the wall occurs in a markedly abnormal manner.

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Clinical Reports

PULSELESS DISEASE*

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PULSELESS disease or Takayasu's disease is seemingly so rarely encountered that clinical reports may be of interest. Therefore, the following case is presented.

CASE REPORT

The patient, a married woman, was born in 1909 and her disease probably started in 1940 when she was 30 years old. Her first symptoms were recognized as pains in her chest and breathlessness on effort. During pregnancy in 1945 her condition improved somewhat, but later it gradually deteriorated until in 1949 when she was admitted for the first time to the Vestfold Sentralsykehus.

From 1949 she has been in the hospital altogether seven times, the last time in May, 1953, and she has been under supervision in the outpatient department at regular intervals. Her symptoms have during these years partly been general, partly local and confined to the heart, the upper extremities, and the central nervous system.

As far as the symptoms are concerned, she has noticed a general, but at times variable malaise. Sometimes she has also been febrile, and her sedimentation rate which all the time has remained high, has varied in the bad and the good periods between 100 mm./hr. and 30 to 40 mm./hr. She has also suffered from a moderate anemia with hemoglobin down to 64 per cent. The anemia has responded well to iron. The leukocytes have in periods increased to 12,000/c.mm. The serum protein has shown a slight increase in the globulin fraction with a serum albumen and globulin both at about 4 Gm. per cent.

The heart symptoms have in the main consisted of tachycardia of 100 to 120 beats per minute. In addition she has had breathlessness and pains in her chest not typical of the pains of angina pectoris. On auscultation one can hear a systolic, somewhat rough murmur and a long diastolic murmur most pronounced over the base of the heart. She has no doubt an aortic incompetence and possibly an associated aortic stenosis. In this connection it may be mentioned that she has never had rheumatic fever, chorea or syphilis and the sero-reactions were negative. Roentgenograms show some enlargement of the left ventricle. An electrocardiogram in 1949 was quite normal, but later it has on many occasions shown a depression of the S-T interval in Leads II and III and in V_5 and V_6.

In 1949, the first symptoms in the upper extremities occurred as a feeling of numbness. Now and again the fingers became waxy pale. She was no longer able to milk the cows, as she got severe pain in her right hand. Since her first stay in the hospital in 1949, one has never been able

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*Editor's note.—This case will be reported in a somewhat different form in the Norwegian language in *Nordisk medicin*. It is published here for the principal reason that it draws attention to European reports; it is the third to appear from Norway.

to feel any arterial pulsation in the upper extremities. She maintains with certainty that until 1947 she had a palpable radial pulse on both sides. Also, it has never been possible to measure the blood pressure in the upper limbs. On the other hand there has always been normal pulsation in the arteries of the lower limbs, i.e., the femoral, the popliteal, the tibialis posterior, and the dorsalis pedis. The blood pressure in the thighs is considerably increased to 250/90 mm. Hg. By oscillometry there was practically no deflection in the right upper arm, and in the left the deflections were very small. In the lower limbs the deflections were normal (Fig. 1). In 1949, on opening

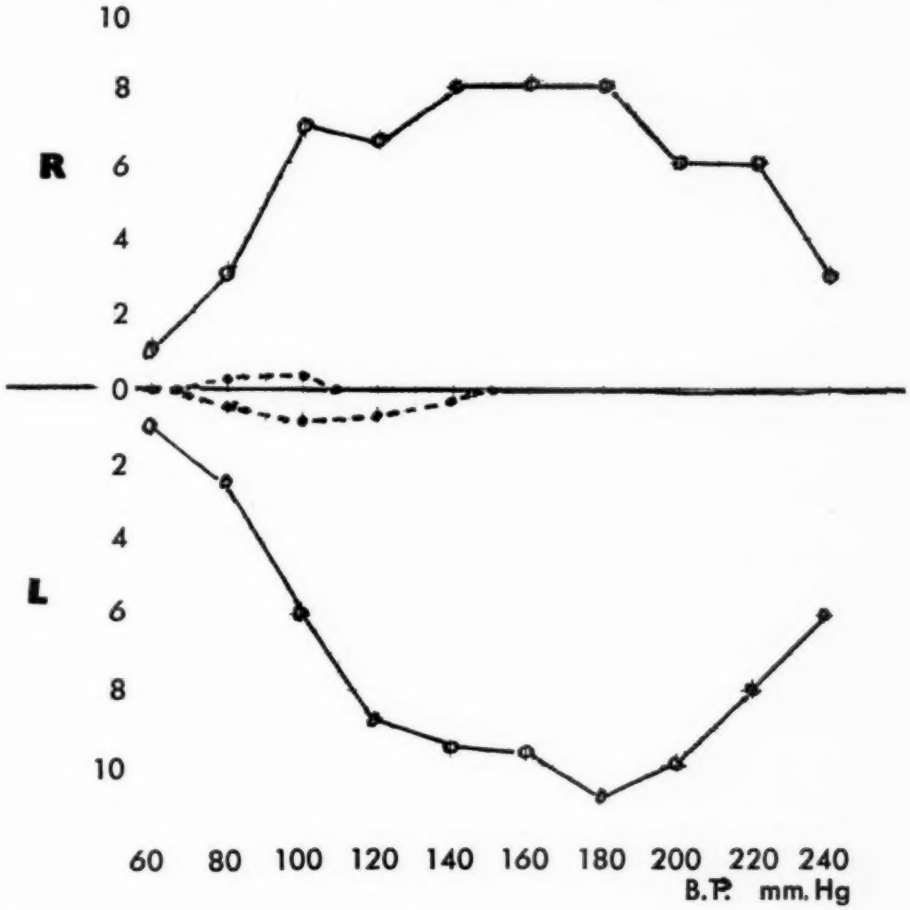

Fig. 1.—Oscillometric tracings from the right and left upper arm and from the legs.
● ——— ● Upper arms
o ——— o Legs

and closing her hands once per second, she suffered severe pains in the right arm and hand after nineteen exercises, and at the same time the right hand and fingers became strikingly pale. Lately the arterial ischemia in the right hand has improved, and on repeating the examination in May, 1953, she could close and open her hands forty times without pain. In 1949, the skin temperature was 2° to 3° C. lower on the right arm and hand than on the left. Another temperature reading taken in May, 1953, showed only a trifling difference on the two sides.

Examination of the neck vessels in 1949 showed a very intense systolic thrill over the right carotid. This thrill has gradually disappeared and at the same time the pulsation has become weaker. It is now weakly palpable on both sides. All the time there has been a rather pro-

nounced soreness over the neck vessels. The soreness which has been somewhat variable, has been most pronounced over the left carotid artery, and there has been the impression of feeling a certain thickening of the vessels.

The cerebral symptoms started in 1951. She suddenly has attacks of vertigo with black-outs, and feeling unsteady she has to sit down or preferably lie down. She also experiences a certain pressure in the head. The attacks which as a rule last a couple of minutes, are often provoked by looking up or getting up quickly or by moving her head quickly. A neurological examination in May, 1953, revealed no abnormalities and the electroencephalogram was normal. An eye examination in May, 1953, revealed normal optic discs and vessels without any alterations of caliber. In the fundi one observed numerous scattered punctate and somewhat larger red spots representing either hemorrhages or small aneurysms. Most of the spots were seen in the periphery of the fundi.

The patient has during her many stays in the hospital received several courses of penicillin in large dosage. She has also been treated with Aureomycin, ACTH and Cortone, and lastly she has received local x-ray treatment for the sore neck vessels. None of these treatments has had any certain effect.

DISCUSSION

In this young woman there have been found signs of a chronic vascular disease which has attacked the vessels arising from the aortic arch and led to a more or less pronounced narrowing of these vessels. This has resulted in loss of pulsation in the arteries of the upper extremities with symptoms of ischemia in the right hand and reduction of pulsation in carotid arteries on both sides, with symptoms of cerebral ischemia. In addition signs of aortic incompetence have been found and possibly aortic stenosis. Furthermore the patient has general symptoms and most strikingly a greatly raised sedimentation rate.

The unusual disease presented by this patient is known from reports in the literature. Recently Caccamise and Whitman[1] have, in addition to a report on a case of their own, referred to fifty-eight cases published in Japanese medical literature. Caccamise and Whitman's case is possibly the first and only case mentioned from the United States. A case, however, reported by Elliott and associates[2] and explained as a vascular anomaly, seems to be a typical case of pulseless disease. In European literature one finds some publications of undoubted cases. Harbitz and Raeder[5] in 1926 described a 37-year-old woman presenting the typical symptoms, and this case seems to be the first reported outside of Japan. In addition, cases have been reported from different countries.[3,4,6-11] In the reports of Frøvig and associates[3,4] is given a very broad account of one case supplied with careful clinical and pathologico-anatomic investigations.

Different names have been applied to the condition. Caccamise and Whitman refer to it as pulseless disease or Takayasu's disease. The name pulseless disease, which first was applied to the condition by Shimidzu,[12] is simple and striking even though only certain arteries are pulseless. Shimidzu has also given the condition the more scientific and very appropriate name thromboarteritis obliterans subclavio-carotica. Frøvig calls it the syndrome of the obliteration of the arterial branches of the aortic arch due to arteritis. This, though in itself a striking designation, is somewhat ponderous. It is supposed that pulseless disease is the name that will suit best.

Pulseless disease may be summarized as follows:

The disease takes a chronic course and occurs mainly in young females. This last statement applies to all cases reported outside Japan, except the case reported by Elliot and associates. Among the cases from Japan referred to by Caccamise and Whitman, the sex is given in forty-four cases, and of these, thirty-nine were females aged 11 to 32 years, and only five were males.

The disease produces general symptoms and most strikingly a highly raised sedimentation rate.

The main affection is a narrowing or complete occlusion of the large arteries that arise from the aortic arch, while all other arteries seem normal. As a consequence one finds a weak or abolished radial and carotid pulse. Symptoms of ischemia in the central nervous system may be of different degrees varying between slight fainting attacks and epileptiform convulsions or serious paralyses. Many patients also present eye symptoms in the way of cataract or fundal changes and particularly characteristic arteriovenous aneurysms. Aortic incompetence and possibly aortic stenosis have been described in this case, but this has apparently never been encountered before.

Histologically one finds an arteritis with considerable inflammatory phenomena, cell infiltration, and frequently giant cells. In addition to this one finds thrombi that must be looked upon as secondary to the arteritis.

As mentioned the course extends over years with progressive symptoms. The usual cause of death is cerebral ischemia caused by thrombi in the carotid arteries.

No treatment is known. Antibiotics ACTH and Cortone in our case had no effect. Chronic treatment with anticoagulants seems feasible, because it is the arterial thrombi that give the serious symptoms. How much is to be gained by such a treatment is, however, uncertain.

As far as the frequency of pulseless disease is concerned it is not improbable, that when the disease is more generally known, it will be diagnosed in increasing numbers.

SUMMARY

A case of pulseless disease is presented. The essential findings were complete loss of pulsation in the arms, reduced pulsation in the carotid arteries, and aortic incompetence.

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ANOMALY OF TOTAL PULMONARY VENOUS CONNECTION

Report of a Case with Survival for 31 Years

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THE anomaly of total pulmonary venous drainage represents one of the two pulmonary venous anomalies classified by Brody in 1942.[1] Whereas patients with anomaly of partial venous drainage empty blood from one lung (usually the right lung) into either the superior vena cava, right atrium, or left innominate vein communicating with the right heart, patients with anomaly of total pulmonary venous drainage empty all the blood from both lungs into the right heart. Since there are no veins emptying into the left atrium, postnatal survival with this anomaly is entirely dependent upon the presence of a patent foramen ovale or interatrial septal defect. However, recent clinical, laboratory and pathologic studies have indicated a need for revision of the terminology of pulmonary venous anomalies. Edwards[2] prefers anomalous pulmonary venous "connection" when the pulmonary veins connect to the right atrium, or systemic veins, rather than to the left atrium. Usually this implies anomalous drainage as well, but an exceptional case reported by Mankin and Burchell[3] showed evidence of anomalous connection of the right pulmonary veins with left superior vena cava and coronary sinus. Since the latter also communicated with the left atrium, there was no anomalous venous drainage in a physiologic sense. Contrariwise, Swan and associates,[4] demonstrated by means of differential dye dilution curves that there is preferential drainage of saturated blood from the right lung into the right atrium in patients with a large atrial septal defect. Thus there may be partial anomalous venous drainage without anomalous venous connection, due to the proximity of the right pulmonary venous orifices to the atrial septum.

Usually there is a striking difference between the clinical manifestation of these two types of anomalous venous connection.[1,2,5] Provided less than 50 per cent of the pulmonary venous blood is returned to the right side of the heart, patients exhibit no defect in growth or development, no cyanosis, may not have any cardiac symptoms, signs, or enlargement, and no apparent shortening of the

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life span. In contrast to these patients, other patients with the anomaly of total pulmonary venous connection often exhibit cyanosis, have one or more other cardiac anomalies, and rarely survive beyond infancy. Brody found case reports of only eight patients that lived beyond 6 months (9 months to 27 years).[1] Since then more patients have been reported as these anomalies are recognized by angiocardiography or cardiac catheterization.[5] Muller has successfully anastomosed the common left pulmonary vein to the appendage of the left atrium in two patients.[6] One of these was a 4-year-old boy with cyanosis and heart failure. He was markedly improved for the duration of the one-year follow-up. The other, a 25-year-old patient, died within 10 hours postoperatively. Since no post-mortem examination was permitted, the cause of death was not established. Two of the patients reported by Snellen and Albers had attained the ages of 20 and 22 years.[8] These authors also emphasized an important diagnostic sign, the figure "8" shape of the cardiac silhouette in the chest roentgenogram, which aids clinical detection of these patients.

The presence of rather definite diagnostic features, plus the unique autopsy findings in a patient that has survived longer than others to date, provides the basis for this case report.

CASE REPORT

R.McC. A Negro woman of 29 years of age was first admitted on Oct. 24, 1951, because of severe palpitations and a history of dyspnea on exertion. She had been in good health all her life until she was 25 years of age, at which time she first became aware of mild fatigue and dyspnea on exertion. During the past 4 years these symptoms had increased and became particularly severe whenever she also experienced episodes of severe palpitation of the heart and dizziness. Her private physician had diagnosed heart disease and given her digitoxin during this period of time. Although she had noted slight ankle edema occasionally, she denied any orthopnea or paroxysmal nocturnal dyspnea. She had another attack of palpitations earlier on the day of entry, and the heart rate was found to be 120 per minute. The ventricular rate promptly slowed to 60 during carotid sinus pressure, but accelerated on release of the pressure. Temperature was 98.6° F.; pulse regular and 88 per minute; respirations, 18 per minute; and blood pressure, 106/70 mm. Hg. There was marked clubbing of the fingers and toes. There was slight cyanosis. The thyroid gland was not palpable. The chest expanded symmetrically, and the lungs were normal. The heart was enlarged almost to the anterior axillary line in the fifth left intercostal space. The second pulmonic sound was louder than the second aortic sound. There was a Grade 2 blowing, systolic murmur at the pulmonic area. The first sound at the apex was split and followed by a Grade 1 systolic murmur. The liver was not palpable. The routine laboratory examination was unremarkable except for a hematocrit of 52 per cent, hemoglobin, 17.5 gram per cent, and an electrocardiograph which showed a semivertical position with balanced rotation of the electric field of the heart. There was normal sinus rhythm with a rate of 70 per minute. The P-R interval was prolonged to 0.25, which constituted a first degree atrioventricular heart block. The P-wave in Lead II was broadened to 0.16 sec. and was notched. The amplitude was slightly more than 0.2 mv. The T waves were inverted in limb Leads II, III, aV_F, and all precordial leads. There was an rSr′ complex in V_1, and the onset of the intrinsicoid deflection in that lead was 0.06 sec. Chest roentgenogram revealed marked enlargement of the cardiac silhouette and accentuation of the pulmonary vascular markings with slight passive congestion of the lung fields. Fluoroscopic examination of the chest revealed poor diaphragmatic excursions and no pleural fluid. The lung fields were clear, and there were very prominent intrinsic expansile pulsations in the hilar shadows. The heart was enlarged both to the right and the left, involving primarily the right atrium and the right ventricle. The barium-filled esophagus showed no significant deviation to either the right or posteriorly. In addition, there was another shadow above the right atrium that gave the heart a figure "8" shape (Fig. 1). This shadow protruded beyond the normal border of the superior vena

cava and showed vigorous expansile pulsations which were distinctly out of phase with those of the pulmonary artery. The asynchronous nature of these pulsations was confirmed by an electrokymographic examination (Fig. 2). The arterial oxygen saturation was 79.5 per cent, and the CO_2 content was 32.7 volume per cent.

Cardiac catheterization was performed utilizing the antecubital vein in the left arm. The catheter readily passed into the chest and the right auricle and then happened to coil in the superior vena cava, filling the pulsating structure previously referred to (Fig. 3). This appeared to be evidence of aneurysmal dilatation of the superior vena cava. The other pertinent data obtained during catheterization are given in Table I.

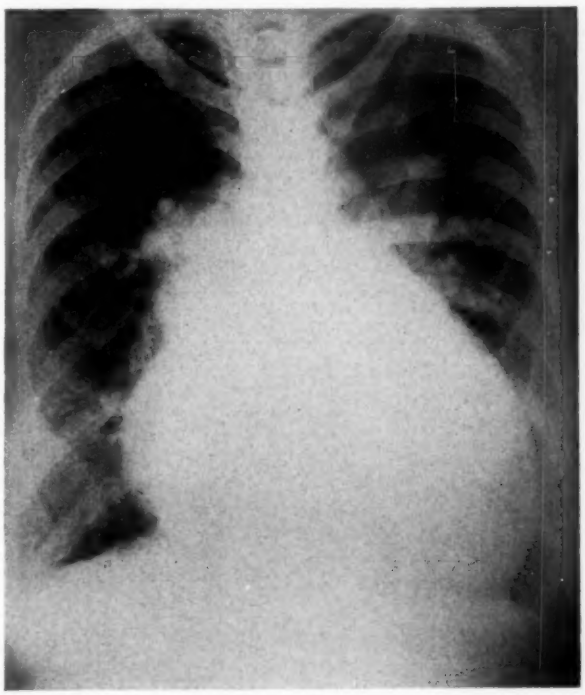


Fig. 1.—Chest roentgenogram of R.McC. (10-17-51) illustrating cardiac enlargement and the characteristic figure "8" shape of the cardiac silhouette due to aneurysmal dilatation of the superior vena cava.

TABLE I

POSITION	OXYGEN CONTENT VOLUME (%)	SATURATION (%)	PRESSURE MM. HG	MEAN MM. HG
Superior vena cava	19.1	95.4	11/3	
Inferior vena cava	12.3	56.4	14/12	
Right atrium	18.0	89.5	11/3	7
Right ventricle	16.6	82.6	48/9	24
Pulmonary artery	17.8	88.8	44/22	
Radial artery	17.5	87.5		
Same, while breathing O_2	18.3	91.0		
Hemoglobin, 15.0 gram per cent				
Oxygen consumption, 138 ml. STPD				
Heart rate, 80				

These data were interpreted to represent the anomaly of partial pulmonary venous connection from the right lung into an aneurysmal dilatation of the superior vena cava. In addition, there was considered to be an interatrial septal defect, largely on the basis of conspicuous unsaturation of radial arterial blood. The lack of any significant right ventricular hypertension was considered to make the possibility of an interventricular septal defect unlikely.

The patient was discharged on Nov. 3, 1951, essentially free of symptoms. She returned to clinic on several occasions because of palpitation. Electrocardiogram revealed atrial flutter which was controlled with digitoxin and quinidine.

The patient was again seen on Feb. 27, 1953. She had pitting edema of the legs and sacral region and presented evidence of ascites. There were a few basilar râles in the lung fields. The heart was slightly larger than on previous occasions. After several days of medical treatment an exercise tolerance test[9] was done on March 12, 1953. She was able to walk for only 1.5 minutes. The blood pressure averaged 113/73 mm. Hg at rest, and fell to 105/62 during exertion, and varied from 100/70 to 90/70 during the next 5 minutes of recovery. There was no tachycardia. Precordial lead electrocardiograms showed a change in T waves from inverted at rest to upright with exertion and early recovery. The physical fitness index was 1.5 (normal range is from 13 to 26).

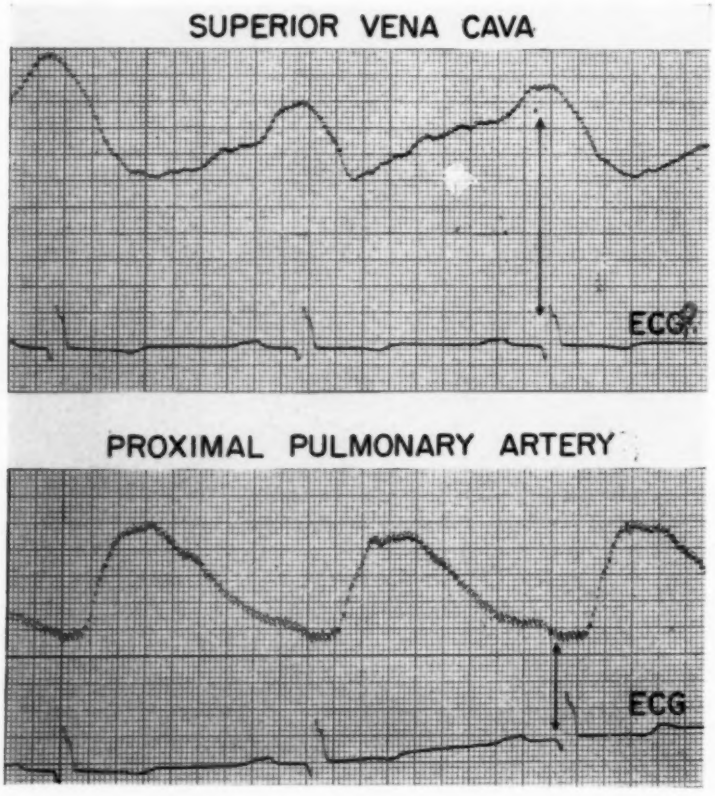


Fig. 2.—Electrokymographic recordings of border motions of superior vena cava and proximal pulmonary artery. Note that the pulsations are not synchronous.

She regained compensation of her heart and was discharged March 25, 1953. She did not adhere to the medical regimen, however, and returned on April 10 with recurrence of congestive heart failure. This time the heart was grossly enlarged, the rhythm was regular and the rate, 160 per minute. The following afternoon she suddenly fainted, became hyperpneic, and perspired freely. On regaining consciousness she complained of vague abdominal discomfort. At 3:00 A.M. on

April 12, she again became weak, sweated freely, and was apprehensive. She had a pounding, irregular pulse. She expired at 4:30 A.M. on April 12, four days before her thirty-first birthday.

Autopsy examination showed slight abdominal distention but no edema. The left pleural cavity contained 400 c.c. of clear, straw-colored fluid and there were about 100 c.c. in the right pleural cavity. The pleural surfaces were smooth and glistening. The left lung weighed 660 grams, and the right lung, 750 grams; both exhibited hyperemia and edema. The pericardium contained 100 c.c. of clear straw-colored fluid. There were no pericardial adhesions. On external examination of the heart there was a small area of shaggy redness approximately 0.5 cm. in diameter over the anterior aspect of the right ventricle. The chambers were extremely dilated in situ. The right ventricle covered the anterior surface. The right auricle was markedly distended. The heart weighed 460 grams. The aortic ring measured 5.5 cm.; the pulmonic ring, 9.0 cm.; tricuspid, 15.5 cm.; and mitral, 9.5 cm. The right ventricular wall measured from 0.3 to 0.6 cm. in thickness. The valves appeared competent. The myocardium was brown-red and of normal

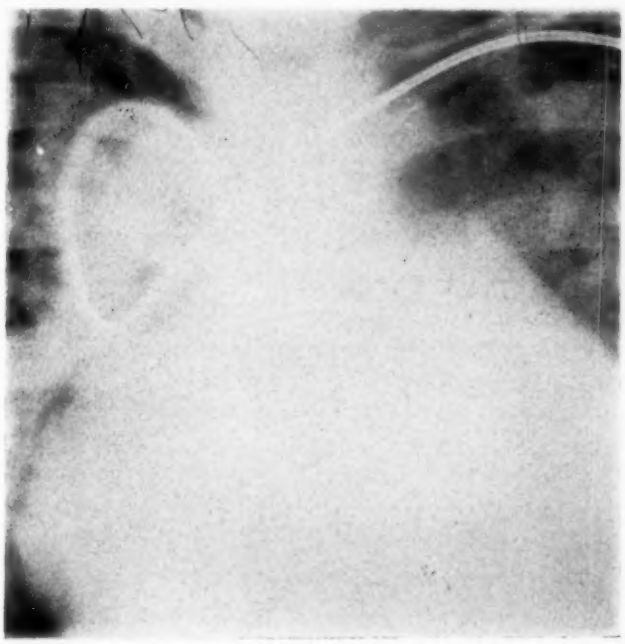
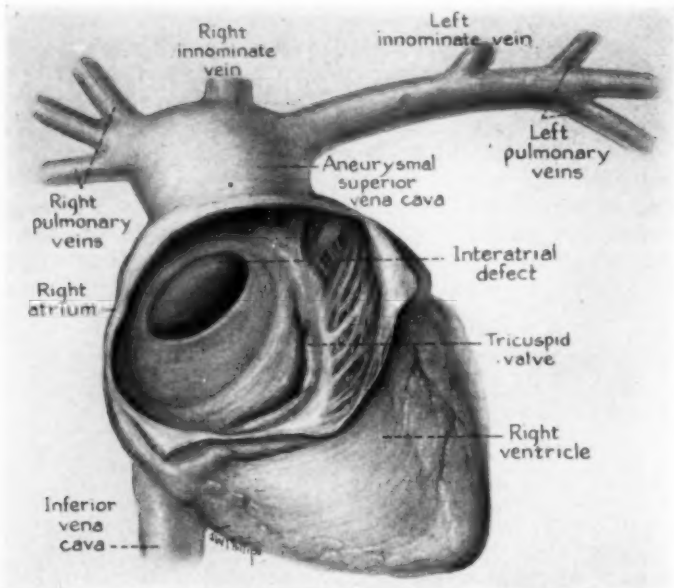
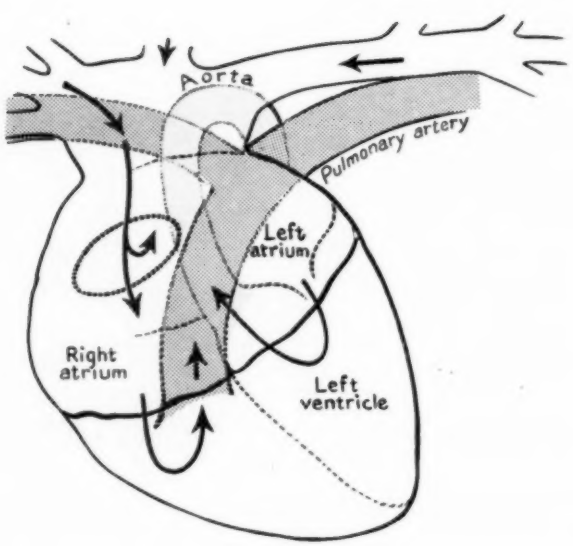


Fig. 3.—Spot film of cardiac catheter fortuitously buckled in aneurysmal dilatation of superior vena cava.

texture. There were three pulmonary veins from the left lung which united in a common vein that passed anteriorly across the aortic arch to an aneurysmal dilatation of the superior vena cava (Fig. 4). This vein measured 6 cm. in length and appeared sufficiently long that it could have been anastomosed to the appendage of the left atrium. There were also three pulmonary veins from the right lung that entered this same aneurysmal sac via a common right vein (Fig. 4). The inferior vena cava entered the right auricle normally. Since there was no pulmonary venous return to the left atrium, this was a small chamber. There was an interatrial septal defect at the superior part of the septum measuring 2.1 by 3.6 cm. which amounted to approximately one-third of the septum. The right ventricle was tremendously dilated. The left ventricle was a small chamber. The aortic ring barely admitted the index finger. The ligamentum arteriosus was identified as a fibrous strand. The coronary arteries were not remarkable. The diameter of the aorta was decreased throughout its entire length. There were no plaques. The intima appeared normal. The liver weighed 1,750 grams. The capsule was whitish. The liver surface was grossly irregular; a deep mottled purple-brown. On cut section, the lobular configuration showed marked distortion and hyperemia.



A.



B.

Fig. 4.—*A*, Anatomic relations of anomaly of total pulmonary venous connection with aneurysmal dilatation of superior vena cava. Note the size and position of the interatrial septal defect. *B*, Schematic sketch of heart and great vessels illustrates a small aorta and large pulmonary artery.

COMMENT

This case is unique since it represents the longest survival on record of a patient with the anomaly of total pulmonary venous connection. Furthermore, the patient was asymptomatic for the first 25 years of her life and had no impairment of growth or development. Survival was entirely dependent upon the presence of an interatrial septal defect which permitted oxygenated blood (even though mixed with unsaturated venous blood) access to the left heart and systemic circulation. Edwards has discussed the importance of the relative size of the defect in relation to that of the tricuspid valve as a significant factor in determining the degree of unsaturation of peripheral arterial blood.[10] A brief perusal of the published cases of patients with anomalous total pulmonary venous drainage suggested the possibility of an optimal size of this interatrial defect being pertinent to the longevity of the patient. Of four patients previously reported who have survived beyond infancy and have been examined at autopsy, three have had either a single atrium or cor biloculare.[11-14] Hence even with a complete absence of the interatrial septum, no patient has survived this long. In this patient, the defect was located in the superior portion of the interatrial septum, nearest the aneurysmal dilatation of the superior vena cava which was connected to the anomalous pulmonary veins. The defect was an elliptical opening 21 by 36 mm. Kernan's patient with a defect of 8 by 11 mm. survived for only 5 months.[15]

This case also confirms the impressions of Snellen and Albers that some of these patients have a characteristic figure "8" shape of the cardiac silhouette by chest roentgenographic examination.[8] This is due to the presence of the aneurysmal dilatation of the superior vena cava. Furthermore, this venous shadow reveals conspicuous pulsations which are out of phase with those arising from the pulmonary artery or aorta (Fig. 2).

The diagnosis of anomaly of total pulmonary venous connection should be suspected whenever this figure "8" pattern of the heart is encountered. Typically the right side of the heart is enlarged, whereas the left side of the heart, especially the atrium, and aorta are either small or within normal limits. Cyanosis may not be marked. The diagnosis may be confirmed by cardiac catheterization when the oxygen content of this venous structure and right atrium roughly equal, or even exceed, that of the peripheral artery.[5,16]

It is important to realize that an unusual patient with this venous anomaly may live for years before showing clinical manifestations of cardiac insufficiency. Once cardiac symptoms develop, however, it is now important to consider surgical treatment. One of the two cases treated by Muller showed marked improvement as a result of anastomosing the common left pulmonary vein to the appendage of the left atrium. The autopsy findings in our case indicate that surgical treatment was feasible, had the proper diagnosis of total rather than partial anomalous pulmonary venous connection been made prior to death. Unfortunately, the unusual age of this patient was given improper weight in excluding the possibility of total anomalous venous connection. Repeating the cardiac catheterization and utilizing the right arm might have permitted recognition of the anomalous

connection of the left pulmonary veins. Finally, the use of dye dilution curves during cardiac catheterization should afford a more satisfactory appraisal of these anomalies in the future.[4]

SUMMARY

1. An unusual case of anomaly of total pulmonary venous connection is reported because of the following features:

(a) freedom from symptoms for 25 years; (b) survival for 31 years (the longest yet reported); (c) characteristic diagnostic features which were not fully appreciated ante mortem; and (d) a large interatrial septal defect, measuring 21 by 36 mm. at autopsy.

2. It is suggested that the unusual longevity is due to the optimal size of the atrial defect.

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Book Reviews

TRAITÉ DES CARDIOPATHIES CONGÉNITALES. Under the direction of E. Donzelot and F. d'Allaines, and by R. Heim de Balsac, C. Métianu, M. Durand, Ch. Dubost, M. Allary, N. du Bouchet, A. M. Emam-Zadé, J. E. Escalle, B. Latscha, J. le Brigand and N. Œconomos. Paris, 1954, Masson & Cie, 1,116 pages, 1,155 illustrations.

This book is an extensive treatise on congenital heart disease and is the first to cover exhaustively the existing knowledge of the subject with a correlation of all the special fields. Embryology, anatomy, and physiology are admirably combined and integrated to the extent that is possible at this time. The authors have utilized their clinical acumen and knowledge of electrocardiography, radiology, angiocardiography, and venous and arterial catheterization, and have reviewed not only the continental but also the world's literature in one large volume. The authors are seasoned clinicians and investigators of the University of Paris and have described in detail the methodology used, together with its usefulness and limitations. Surgical correction of the various lesions is described, and an evaluation of present-day surgery is discussed.

This book should be on the library shelf of all who are engaged in the study of patients with congenital heart disease.

L. D.

GOURMET COOKING FOR CARDIAC DIETS. By Florence Field. Introduction by Harold Feil, M.D., Cleveland and New York, 1953, The World Publishing Company, 338 pages.

This is a cookbook of appetizing foods for cardiac patients and others who should reduce. It is simple and practical in its composition. The reviewer has tried several of the recipes and found the dishes palatable.

In addition to weight-reducing and sodium-restricted diets, there are also recipes allowed with a low-fat, low-cholesterol diet and a low-purine diet for gouty patients. It contains the necessary theoretical background material which should be known both to cook and patient, how the individual foods should be handled and also tables indicating contents of calories, sodium, etc., timetables for cooking and ideal weights. There is in it a wealth of material not readily found elsewhere.

The book goes a long way to relieve the monotony of these diets which has been one of the principal obstacles to their success in the past. It should be familiar to every internist for its use will greatly facilitate the management of cardiovascular patients.

J. J.

AUTOPSY DIAGNOSIS OF CONGENITALLY MALFORMED HEARTS. By Maurice Lev. Springfield, Ill., 1953, Charles C Thomas, Publisher, 180 pages.

This little book is limited in its scope but excellent in its execution. It is a prosector's manual for dissection of congenitally malformed hearts. It has a short introduction describing the technique best applicable to these conditions. There is a catalogue of the individual abnormalities and a description of the combinations in which they are most frequently found. There is also a comprehensive bibliography.

To the clinician the book is a valuable supplement to the larger texts on the subject but it does not supplant them, for it limits itself strictly to anatomic descriptions of the various conditions and a short discussion of the pathogenesis of the more important ones without reference to the clinical aspects.

The book is richly and beautifully illustrated. It can be recommended unreservedly for its limited purpose.

J. J.

Announcements

THE AMERICAN COLLEGE OF CARDIOLOGY will hold its third annual convention at the Conrad Hilton Hotel in Chicago, May 27 to 29, 1954. An interesting scientific program has been arranged for this meeting. The topic will be "Prognosis of Heart Disease." Guest speakers of national prominence will cover all aspects of cardiac prognosis. In addition to the scientific sessions there will be scientific exhibits on cardiovascular research and commercial exhibits, outlining the latest advances in the field of cardiology. Any further information, pertaining to the program may be obtained from the Secretary of the College, Dr. Philip Reichert, 140 West 57th Street, New York 19, N. Y.

THE GRADUATE SCHOOL OF MEDICINE OF THE UNIVERSITY OF PENNSYLVANIA announces the inauguration of an eight month full-time basic course in cardiology to begin on Sept. 28, 1954. This course, which will be given under the direction of Prof. William D. Stroud, will cover the fundamentals of cardiovascular medicine and has been planned to provide a foundation for residency and other clinical training leading to qualifications for the practice of cardiology as a specialty. The initial course will be limited to ten students, and preference will be given to those candidates who have either qualified for certification by the American Board of Internal Medicine or are working towards such qualification. For detailed information inquiries should be addressed to the Dean, Graduate School of Medicine, 238 Medical Laboratories Building, University of Pennsylvania, Philadelphia 4, Pa.

On Sept. 9 and 10, 1954, a SEMINAR on CARDIAC ARRHYTHMIAS, sponsored by the University of Vermont College of Medicine and the Vermont Heart Association, will be held in Burlington, Vermont. It will be conducted by Dr. E. Lepeschkin, with Dr. D. Scherf and Dr. S. Bellet, as guest speakers. It is planned to give seven hours of lectures and demonstrations each day in the morning and late evening, with the afternoon left free for excursions to Lake Champlain and the Green Mountains. Participants are urged to bring difficult electrocardiograms for discussion. Participants not connected with the University of Vermont will be charged $10 to cover expenses. Further information can be obtained from Dr. Lepeschkin, Division of Experimental Medicine, University of Vermont College of Medicine, Burlington, Vermont.

On Sept. 11, 1954, a SYMPOSIUM ON THE U WAVE OF THE ELECTROCARDIOGRAM will be held at the Oakledge Manor, Burlington, Vermont, on the shore of Lake Champlain. It will be sponsored by the University of Vermont College of Medicine and the Vermont Heart Association, and will be conducted by Dr. E. Lepeschkin. Dr. H. Hecht, Dr. J. H. Palmer, and Dr. M. Segers will be among the speakers. There will be no registration fee. All interested in presenting a paper of about fifteen minutes' duration on this subject are invited to communicate the title and the preference as to time of day to Dr. E. Lepeschkin, Division of Experimental Medicine, University of Vermont College of Medicine, Burlington, Vermont, who will furnish further particulars. It is planned to publish the proceedings of the Symposium in monograph form.